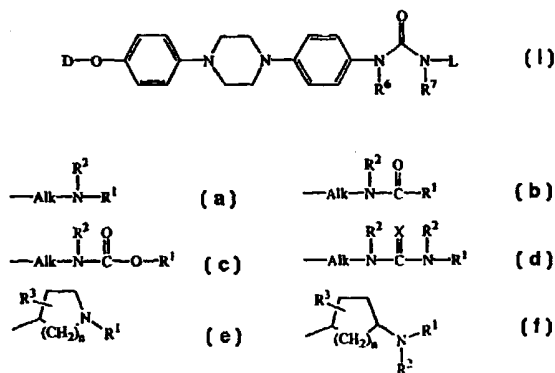




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(21) International Application Number: PCT/EP99/03242 (22) International Filing Date: 6 May 1999 (06.05.99) (30) Priority Data: 98201588.5 14 May 1998 (14.05.98) EP (71) Applicant (for all designated States except US): JANSSEN PHARMACEUTICA N.V. [BE/BE]; Patent Dept., Turnhoutseweg 30, B-2340 Beerse (BE). (72) Inventors; and (75) Inventors/Applicants (for US only): MEERPOEL, Lieven [BE/BE]; Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2340 Beerse (BE). BACKX, Leo, Jacobus, Jozef [BE/BE]; Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2340 Beerse (BE). VAN DER VEKEN, Louis, Jozef, Elisabeth [BE/BE]; Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2340 Beerse (BE). (74) Agent: DAELEMANS, Frank; Janssen Pharmaceutica N.V., Patent Dept. - ext. 5476, Turnhoutseweg 30, B-2340 Beerse (BE).		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>

(54) Title: WATER SOLUBLE AZOLES AS BROAD-SPECTRUM ANTIFUNGALS



(57) Abstract

The present invention concerns novel compounds of formula (I) the *N*-oxide forms, the pharmaceutically acceptable addition salts and stereochemically isomeric forms thereof, wherein L represents a radical of formulae (a), (b), (c), (d), (e), or (f); wherein each Alk independently represents an optionally substituted C₁₋₆alkanedyl; n is 1, 2 or 3; Y is O, S or NR²; R¹ represents aryl, Het¹, or an optionally substituted C₁₋₆alkyl; R² represents hydrogen; or in case R¹ and R² are attached to the same nitrogen atom, they may be taken together to form a heterocyclic radical; or they may be taken together to form an azido radical; each R³ independently represents hydrogen, hydroxy or C₁₋₄alkyloxy; aryl represents phenyl, naphthalenyl, 1,2,3,4-tetrahydronaphthalenyl, indenyl or indanyl; each of said aryl groups may optionally be substituted; Het¹ represents an optionally substituted monocyclic or bicyclic heterocyclic radical; Het² is the same as Het¹ and may also be piperazinyl, homopiperazinyl, 1,4-dioxanyl, morpholinyl, thiomorpholinyl; R⁶ represents hydrogen or C₁₋₄alkyl; R⁷ represents hydrogen or C₁₋₄alkyl; or R⁶ and R⁷ taken together form a bivalent radical of formula -N=CH- (i), -CH=N- (ii), -CH=CH- (iii), -CH₂-CH₂ (iv), wherein one hydrogen atom in the radicals (i) and (ii) may be replaced with a C₁₋₄alkyl radical and one or more hydrogen atoms in radicals (iii) and (iv) may be replaced by a C₁₋₄alkyl radical and; D represents a trisubstituted tetrahydrofuran derivative; as antifungals; their processes for preparation, compositions containing them and their use as a medicine.

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WATER SOLUBLE AZOLES AS BROAD-SPECTRUM ANTIFUNGALS

5 The present invention is concerned with water soluble azoles as broad-spectrum antifungals and their preparation; it further relates to compositions comprising them, as well as their use as a medicine.

10 Systemic fungal infections in man are relatively rare in temperate countries and many of the fungi that can become pathogenic normally live commensally in the body or are common in the environment. The past few decades have witnessed an increasing incidence of numerous life-threatening systemic fungal infections world-wide and these now represent a major threat to many susceptible patients, particularly those already hospitalized. Most of the increase can be attributed to improved survival of immuno-
15 compromised patients and the chronic use of antimicrobial agents. Moreover, the flora typical of many common fungal infections is also changing and this is presenting an epidemiological challenge of increasing importance. Patients at greatest risk include those with impaired immune functioning, either directly as a result of immuno-
20 suppression from cytotoxic drugs or HIV infection, or secondary to other debilitating diseases such as cancer, acute leukaemia, invasive surgical techniques or prolonged exposure to antimicrobial agents. The most common systemic fungal infections in man are candidosis, aspergillosis, histoplasmosis, coccidioidomycosis, paracoccidioidomycosis, blastomycosis and cryptococcosis.

25 Antifungals such as ketoconazole, itraconazole and fluconazole are employed for the treatment and prophylaxis of systemic fungal infections in immunocompromised patients. However, concern is growing about fungal resistance to some of these agents, especially these with a relatively narrow spectrum, e.g. fluconazole. Worse still, it is recognized in the medical world that about 40% of the people suffering from severe
30 systemic fungal infections are hardly, or not at all, able to receive medication via oral administration. This inability is due to the fact that such patients are in coma or suffer from severe gastroparesis. Hence, the use of insoluble or sparingly soluble antifungals such as itraconazole, that are difficult to administer intravenously, is heavily impeded in this group of patients.

35

Also the treatment of onychomycosis may well be served by potent water soluble antifungals. It is long desired to treat onychomycosis via the transungual route. The

-2-

problem that then arises is to ensure that the antifungal agents will penetrate into and beneath the nail. Mertin and Lippold (J. Pharm. Pharmacol. (1997), 49, 30-34) stated that in order to screen for drugs for topical application to the nail plate, attention has to be paid mainly to the water solubility of the compound. The maximum flux through the nail is beneficially influenced by increasing the water solubility of the antifungal. Of course, efficacy in treating onychomycosis via the transungual route is also dependent on the potency of the antifungal.

Consequently, there is a need for new antifungals, preferably broad-spectrum antifungals, against which there is no existing resistance and which can be administered intravenously or transungually. Preferably the antifungal should also be available in a pharmaceutical composition suitable for oral administration. This enables the physician to continue treatment with the same drug after the patient has recovered from the condition which required intravenous or transungual administration of said drug.

US-4,267,179 discloses heterocyclic derivatives of (4-phenylpiperazin-1-yl-aryloxy-methyl-1,3-dioxolan-2-yl)-methyl-1*H*-imidazoles and 1*H*-1,2,4-triazoles useful as antifungal agents. Said patent encompasses itraconazole, which is available as a broad-spectrum antifungal on a world-wide basis.

WO 93/19061 discloses the [2*R*-[2 α ,4 α ,4(*R*^{*})]], [2*R*-[2 α ,4 α ,4(*S*^{*})]], [2*S*-[2 α ,4 α ,4(*S*^{*})]] and [2*S*-[2 α ,4 α ,4(*R*^{*})]] stereospecific isomers of itraconazole, which are taught to have greater water solubility than the respective diastereomeric mixtures thereof.

WO 95/19983 discloses derivatives of [[4-[4-(4-phenyl-1-piperazinyl) phenoxy-methyl]-1,3-dioxolan-2-yl]methyl]-1*H*-imidazoles and 1*H*-1,2,4-triazoles, structurally related to some of the compounds of the present invention, which are taught to be water-soluble antimicrobial agents.

WO 95/17407 discloses tetrahydrofuran antifungals as well as WO 96/38443 and WO 97/00255. The latter two publications disclose tetrahydrofuran antifungals, which are taught to be soluble and/or suspensible in an aqueous medium suitable for intravenous administration, containing substitution groups readily convertible *in vivo* into hydroxy groups.

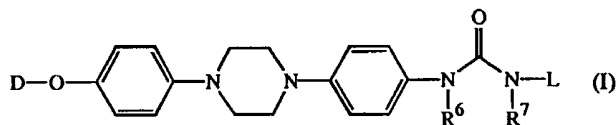
Saksena et al. in Bioorg. Med. Chem. Lett. (1995), 5(2), 127-132, discloses some tetrahydrofuran basedazole antifungals such as (3*R*-cis)- 4-[4-[4-[[5-(2,4-difluorophenyl)tetrahydro-5-(1*H*-1,2,4-triazol-1-ylmethyl)-3-furanyl]methoxy]phenyl]-1-piperazinyl]phenyl]-2-[2-(dimethylamino)ethyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-one. Saksena et al. reported of saidazole that, when compared to SCH 51048, it was

profoundly less active as antifungal.

Unexpectedly, the compounds of the present invention are potent broad-spectrum antifungals with good water solubility.

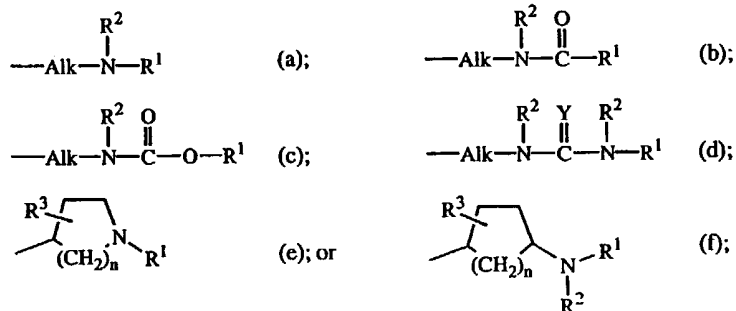
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The present invention concerns compounds of formula



the *N*-oxide forms, the pharmaceutically acceptable addition salts and stereochemically isomeric forms thereof, wherein

10 L represents a radical of formula



wherein each Alk independently represents C₁₋₆alkanediyl optionally substituted with hydroxy or C₁₋₄alkyloxy;

each n independently is 1, 2 or 3;

15 Y represents O, S or NR²;

each R¹ independently represents aryl, Het¹, or C₁₋₆alkyl optionally substituted with one, two or three substituents each independently selected from halo, hydroxy, mercapto, C₁₋₄alkyloxy, C₁₋₄alkylthio, aryloxy, arylthio, aryl-C₁₋₄alkyloxy, arylC₁₋₄alkylthio, cyano, amino, mono- or di(C₁₋₄alkyl)amino, mono- or di(aryl)amino, mono- or di(arylC₁₋₄alkyl)amino, C₁₋₄alkyloxy-carbonylamino, benzyloxycarbonylamino, aminocarbonyl, carboxyl, C₁₋₄alkyloxy-carbonyl, guanidiny, aryl or Het²;

each R² independently represents hydrogen; or

in case R^1 and R^2 are attached to the same nitrogen atom, they may be taken

25 together to form a heterocyclic radical selected from morpholinyl, pyrrolidinyl, piperidinyl, homopiperidinyl or piperazinyl; said heterocyclic radical may optionally be substituted with C₁₋₄alkyl, aryl, Het², arylC₁₋₄alkyl, Het²C₁₋₄alkyl, hydroxyC₁₋₄alkyl, amino, mono- or

-4-

di(C₁₋₄alkyl)amino, aminoC₁₋₄alkyl, mono- or di(C₁₋₄alkyl)aminoC₁₋₄alkyl, carboxyl, aminocarbonyl, C₁₋₄alkyloxycarbonyl, C₁₋₄alkyloxycarbonylamino or mono- or di(C₁₋₄alkyl)aminocarbonyl; or

they may be taken together to form an azido radical;

5 each R³ independently represents hydrogen, hydroxy or C₁₋₄alkyloxy;

aryl represents phenyl, naphthalenyl, 1,2,3,4-tetrahydro-naphthalenyl, indenyl or indanyl; each of said aryl groups may optionally be substituted with one or more substituents selected from halo, C₁₋₄alkyl, hydroxy, C₁₋₄alkyloxy, nitro, amino, trifluoromethyl, hydroxyC₁₋₄alkyl, C₁₋₄alkyloxyC₁₋₄alkyl, aminoC₁₋₄alkyl, mono- or
10 di(C₁₋₄alkyl)aminoC₁₋₄alkyl;

Het¹ represents a monocyclic or bicyclic heterocyclic radical; said monocyclic heterocyclic radical being selected from the group pyridinyl, piperidinyl, homopiperidinyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, triazolyl, pyranyl, tetrahydropyranyl, imidazolyl, imidazoliny, imidazolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl,
15 thiazolyl, thiazolidinyl, isothiazolyl, oxazolyl, oxazolidinyl, isoxazolyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, furanyl, tetrahydrofuranly, thienyl, thiolanyl, dioxolanyl; said bicyclic heterocyclic radical being selected from the group quinolinyl, 1,2,3,4-tetrahydro-quinolinyl, isoquinolinyl, quinoxalinyl, quinazolinyl, phtalazinyl, cinnolinyl, chromanyl, thiochromanyl, 2H-chromenyl, 1,4-benzodioxanyl, indolyl, isindolyl, indoliny, indazolyl, purinyl, pyrrolopyridinyl, furanopyridinyl,
20 thienopyridinyl, benzothiazolyl, benzoxazolyl, benzisothiazolyl, benzisoxazolyl, benzimidazolyl, benzofuranly, benzothienyl; whereby each of said mono- or bicyclic heterocycle may optionally be substituted with one or where possible more substituents selected from halo, C₁₋₄alkyl, hydroxy, C₁₋₄alkyloxy, nitro, amino, trifluoromethyl, hydroxyC₁₋₄alkyl, C₁₋₄alkyloxy-C₁₋₄alkyl, aminoC₁₋₄alkyl, mono- or
25 di(C₁₋₄alkyl)aminoC₁₋₄alkyl, aryl or arylC₁₋₄alkyl;

Het² is the same as Het¹ and may also be a monocyclic heterocycle selected from piperazinyl, homopiperazinyl, 1,4-dioxanyl, morpholinyl, thiomorpholinyl; whereby each of said monocyclic heterocycle may optionally be substituted with one or where
30 possible more substituents selected from halo, C₁₋₄alkyl, hydroxy, C₁₋₄alkyloxy, nitro, amino, trifluoromethyl, hydroxyC₁₋₄alkyl, C₁₋₄alkyloxyC₁₋₄alkyl, aminoC₁₋₄alkyl, mono- or di-(C₁₋₄alkyl)aminoC₁₋₄alkyl, aryl or arylC₁₋₄alkyl;

R⁶ represents hydrogen or C₁₋₄alkyl;

R⁷ represents hydrogen or C₁₋₄alkyl; or

35 R⁶ and R⁷ taken together form a bivalent radical of formula -R⁶-R⁷- wherein -R⁶-R⁷- is :

-N=CH- (i),

-CH=N- (ii),

-5-

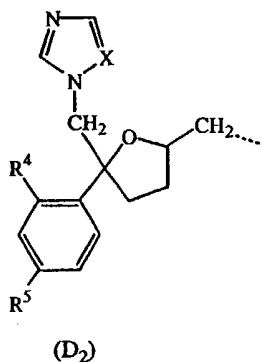
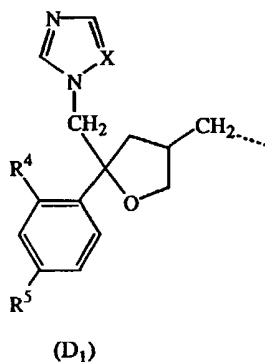
-CH=CH- (iii),

-CH₂-CH₂ (iv),

wherein one hydrogen atom in the radicals (i) and (ii) may be replaced with a C₁₋₄alkyl radical and one or more hydrogen atoms in radicals (iii) and (iv) may be

5 replaced by a C₁₋₄alkyl radical;

D represents a radical of formula



wherein X is N or CH;

R⁴ is hydrogen or halo;

10 R⁵ is halo.

As used in the foregoing definitions and hereinafter halo defines fluoro, chloro, bromo and iodo; C₁₋₄alkyl encompasses the straight and branched chained saturated hydrocarbon radicals having from 1 to 4 carbon atoms such as, for example, methyl, ethyl, propyl, butyl and the like; C₁₋₆alkyl encompasses the straight and branched chained saturated hydrocarbon radicals as defined in C₁₋₄alkyl as well as the higher homologues thereof containing 5 or 6 carbon atoms such as, for example, pentyl or hexyl; C₁₋₆alkanediyl encompasses the straight and branched chained saturated bivalent hydrocarbon radicals having from 1 to 6 carbon atoms such as, for example, methylene, 1,2-ethanediyl, 1,3-propanediyl, 1,4-butanediyl, 1,5-pentanedyl, 1,6-hexanediyl, 1,2-propanediyl, 1,2-butanediyl, 2,3-butanediyl and the like.

The pharmaceutically acceptable addition salts as mentioned hereinabove are meant to comprise the therapeutically active non-toxic acid addition salt forms which the compounds of formula (I) are able to form. The latter can conveniently be obtained by treating the base form with such appropriate acids as inorganic acids, for example, hydrohalic acids, e.g. hydrochloric, hydrobromic and the like; sulfuric acid; nitric acid; phosphoric acid and the like; or organic acids, for example, acetic, propanoic, hydroxyacetic, 2-hydroxypropanoic, 2-oxopropanoic, oxalic, malonic, succinic, maleic, fumaric,

malic, tartaric, 2-hydroxy-1,2,3-propanetricarboxylic, methanesulfonic, ethanesulfonic, benzenesulfonic, 4-methylbenzenesulfonic, cyclohexanesulfamic, 2-hydroxybenzoic, 4-amino-2-hydroxybenzoic and the like acids. Conversely the salt form can be converted by treatment with alkali into the free base form.

5

The compounds of formula (I) containing acidic protons may be converted into their therapeutically active non-toxic metal or amine addition salt forms by treatment with appropriate organic and inorganic bases. Appropriate base salt forms comprise, for example, the ammonium salts, the alkali and earth alkaline metal salts, e.g. the lithium, sodium, potassium, magnesium, calcium salts and the like, salts with organic bases, e.g. the benzathine, *N*-methyl-D-glucamine, 2-amino-2-(hydroxymethyl)-1,3-propanediol, hydrabamine salts, and salts with amino acids such as, for example, arginine, lysine and the like. Conversely the salt form can be converted by treatment with acid into the free acid form.

10

The term addition salt also comprises the hydrates and solvent addition forms which the compounds of formula (I) are able to form. Examples of such forms are e.g. hydrates, alcoholates and the like.

15

The term "stereochemically isomeric forms" as used hereinbefore defines all the possible stereoisomeric forms in which the compounds of formula (I) exist, thus, also including all enantiomers, enantiomeric mixtures and diastereomeric mixtures. Unless otherwise mentioned or indicated, the chemical designation of compounds denotes the mixture of all possible stereoisomeric forms, said mixtures containing all diastereomers and enantiomers of the basic molecular structure. The same applies to the intermediates as described herein, used to prepare end products of formula (I).

20

25

Pure stereoisomeric forms of the compounds and intermediates as mentioned herein are defined as isomers substantially free of other enantiomeric or diastereomeric forms of the same basic molecular structure of said compounds or intermediates. In particular, the term 'stereoisomerically pure' being equivalent to 'chirally pure' concerns compounds or intermediates having a stereoisomeric excess of at least 80% (*i.e.* minimum 90% of one isomer and maximum 10% of the other possible isomers) up to a stereoisomeric excess of 100% (*i.e.* 100% of one isomer and none of the other), more in particular, compounds or intermediates having a stereoisomeric excess of 90% up to 100%, even more in particular having a stereoisomeric excess of 94% up to 100% and most in particular having a stereoisomeric excess of 97% up to 100%. The terms 'enantiomerically pure' and 'diastereomerically pure' should be understood in a similar

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-7-

way, but then having regard to the enantiomeric excess, respectively the diastereomeric excess of the mixture in question.

The terms *cis* and *trans* are used herein in accordance with Chemical Abstracts

5 nomenclature and refer to the position of the substituents on a ring moiety, more in particular on the tetrahydrofuran ring in the compounds of formula (I). For instance, when establishing the *cis* or *trans* configuration of the tetrahydrofuran ring in a radical of formula (D₁), the substituent with the highest priority on the carbon atom in the 2 position of the tetrahydrofuran ring, and the substituent with the highest priority on the
10 carbon atom in the 4 position of the tetrahydrofuran ring are considered (the priority of a substituent being determined according to the Cahn-Ingold-Prelog sequence rules). When said two substituents with highest priority are at the same side of the ring then the configuration is designated *cis*, if not, the configuration is designated *trans*.

15 The compounds of formula (I) all contain at least 2 asymmetric centers which may have the *R*- or *S*-configuration. As used herein, the stereochemical descriptors denoting the stereochemical configuration of each of the 2 or more asymmetric centers are also in accordance with Chemical Abstracts nomenclature.

Of some compounds of formula (I) and of intermediates used in their preparation, the
20 absolute stereochemical configuration was not experimentally determined. In those cases the stereoisomeric form which was first isolated is designated as "A" and the second as "B", without further reference to the actual stereochemical configuration. However, said "A" and "B" stereoisomeric forms can be unambiguously characterized by for instance their optical rotation in case "A" and "B" have an enantiomeric
25 relationship. A person skilled in the art is able to determine the absolute configuration of such compounds using art-known methods such as, for example, X-ray diffraction. In case "A" and "B" are stereoisomeric mixtures, they can be further separated whereby the respective first fractions isolated are designated "A1" and "B1" and the second as "A2" and "B2", without further reference to the actual stereochemical configuration.

30 The *N*-oxide forms of the present compounds are meant to comprise the compounds of formula (I) wherein one or several nitrogen atoms are oxidized to the so-called *N*-oxide.

Whenever used hereinafter, the term "compounds of formula (I)" is meant to also
35 include their *N*-oxide forms, their pharmaceutically acceptable addition salts, and their stereochemically isomeric forms.

Within the scope of the present invention, R⁶ and R⁷ are suitably taken together to form

-8-

$-R^6-R^7$ - which suitably is a radical of formula (ii).

D is suitably a radical of formula D_1 .

X is suitably N.

R^2 is suitably hydrogen.

- 5 R^4 and R^5 suitably are identical, preferably chloro or fluoro. In particular, both R^4 and R^5 are fluoro.

Aryl is suitably phenyl.

- Het¹ is suitably a monocyclic heterocyclic radical; preferably, pyridinyl, piperidinyl, pyrazinyl, pyrimidinyl, pyridazinyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, pyrrolyl, furanyl, tetrahydrofuranyl or thienyl, each of said
 10 monocyclic heterocycles may optionally be substituted with one or where possible more substituents selected from halo, C_{1-4} alkyl, hydroxy, C_{1-4} alkyloxy, nitro, amino, trifluoromethyl, hydroxy C_{1-4} alkyl, C_{1-4} alkyloxy- C_{1-4} alkyl, amino C_{1-4} alkyl, mono- or di(C_{1-4} alkyl)amino- C_{1-4} alkyl; more preferably pyridinyl, piperidinyl or
 15 tetrahydrofuranyl.

An interesting group of compounds within the present invention are those compounds of formula (I) wherein L represents a radical of formula (a), (b) or (c), especially a radical of formula (a).

20

Another interesting group are those compounds of formula (I) wherein Alk is C_{1-6} alkanediyl; particularly, 1,2-ethanediyl, 1,2-propanediyl, 2,3-propanediyl, 1,2-butanediyl, 3,4-butanediyl, 2,3-butanediyl, 2,3-pentanediyl and 3,4-pentanediyl; especially 2,3-butanediyl, 2,3-pentanediyl and 3,4-pentanediyl.

25

Yet another interesting group contains those compounds of formula (I) wherein L is a radical of formula (a) particularly wherein R^1 represents C_{1-6} alkyl optionally substituted with hydroxy or aryl and R^2 represents hydrogen.

- 30 Particular compounds are those compounds of formula (I) wherein R^6 and R^7 are taken together to form $-R^6-R^7$ - which is a radical of formula (ii) and D is a radical of formula D_1 wherein R^4 and R^5 both are fluoro and X is N; more in particular, a radical of formula D_1 wherein the tetrahydrofuran ring has a *cis* configuration.

- 35 Other particular compounds are those compounds of formula (I) wherein L represents a radical of formula (a) wherein R^2 is hydrogen and R^1 represents aryl or C_{1-6} alkyl optionally substituted with one, two or three substituents each independently selected from hydroxy, C_{1-4} alkyloxy, aryloxy, aryl C_{1-4} alkyloxy, cyano, amino, mono- or

-9-

di(C₁₋₄alkyl)amino, mono- or di(arylC₁₋₄alkyl)amino, aminocarbonyl, aryl or Het²; or R¹ and R² taken together with the nitrogen atom to which they are attached form a morpholinyl, pyrrolidinyl, piperidinyl or piperazinyl; said heterocyclic radical may optionally be substituted with C₁₋₄alkyl, aryl, arylC₁₋₄alkyl, hydroxyC₁₋₄alkyl, amino, 5 mono- or di(C₁₋₄alkyl)amino, mono- or di(C₁₋₄alkyl)aminoC₁₋₄alkyl or C₁₋₄alkyloxy-carbonylamino; or R¹ and R² taken together with the nitrogen atom to which they are attached form an azido radical.

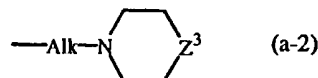
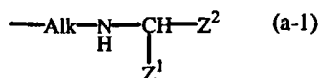
Yet other particular compounds are those compounds of formula (I) wherein L 10 represents a radical of formula (a), (e) or (f), especially a radical of formula (a), wherein R¹ represents aryl, Het¹, or C₁₋₆alkyl substituted with at least one of the substituents selected from aryloxy, arylthio, arylC₁₋₄alkyloxy, arylC₁₋₄alkylthio, mono- or di(aryl)-amino, mono- or di(arylC₁₋₄alkyl)amino, benzyloxycarbonylamino, aryl or Het²; more 15 in particular, wherein R¹ represents aryl or C₁₋₆alkyl substituted with at least one of the substituents selected from aryloxy, arylC₁₋₄alkyloxy, mono- or di(arylC₁₋₄alkyl)amino, aryl or Het².

A preferred group of compounds contains those compounds of formula (I) wherein R⁶ and R⁷ are taken together to form -R⁶-R⁷- which is a radical of formula (ii); D is a 20 radical of formula D₁ wherein R⁴ and R⁵ both are fluoro and X is N; and L represents a radical of formula (a) wherein R² is hydrogen and R¹ represents aryl or C₁₋₆alkyl optionally substituted with one, two or three substituents each independently selected from hydroxy, C₁₋₄alkyloxy, aryloxy, arylC₁₋₄alkyloxy, cyano, amino, mono- or 25 di(C₁₋₄alkyl)amino, mono- or di(arylC₁₋₄alkyl)amino, aminocarbonyl, aryl or Het²; or R¹ and R² taken together with the nitrogen atom to which they are attached form a morpholinyl, pyrrolidinyl, piperidinyl or piperazinyl; said heterocyclic radical may optionally be substituted with C₁₋₄alkyl, aryl, arylC₁₋₄alkyl, hydroxyC₁₋₄alkyl, amino, 30 mono- or di(C₁₋₄alkyl)amino, mono- or di(C₁₋₄alkyl)aminoC₁₋₄alkyl or C₁₋₄alkyloxycarbonylamino.

A more preferred group of compounds are those compounds of formula (I) wherein R⁶ and R⁷ are taken together to form -R⁶-R⁷- which is a radical of formula (ii); D is a 35 radical of formula D₁ wherein R⁴ and R⁵ both are fluoro and X is N; and L represents a radical of formula (a) wherein R² is hydrogen and R¹ represents C₁₋₆alkyl optionally substituted with hydroxy or aryl.

Also preferred is the group of compounds comprising those compounds of formula (I) wherein L is a radical of formula

-10-



wherein Alk is as defined above but preferably is 1,2-ethanediyl, 1,2-propanediyl, 2,3-propanediyl, 1,2-butanediyl, 3,4-butanediyl, 2,3-butanediyl, 2,3-pentanediyl or 3,4-pentanediyl;

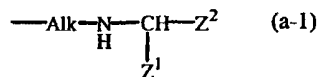
Z¹ is aryl, arylmethyl, arylethyl, Het¹ or C₁₋₄alkyl but preferably is optionally substituted phenyl or optionally substituted phenylmethyl, isopropyl or *tert*-butyl;

Z² is hydrogen, carboxyl, C₁₋₄alkyloxycarbonyl, aminocarbonyl or methyl optionally substituted with hydroxy, methoxy, amino or mono- or di(methyl)amino but preferably is hydrogen, methyl or hydroxymethyl;

or Z¹ and Z² taken together with the carbon atom to which they are attached form a piperidinyl ring substituted with arylmethyl, arylethyl or C₁₋₄alkyl;

Z³ is O, N-C₁₋₄alkyl or N-aryl.

- 15 A particularly preferred group of compounds comprises those compounds of formula (I) wherein L is a radical of formula



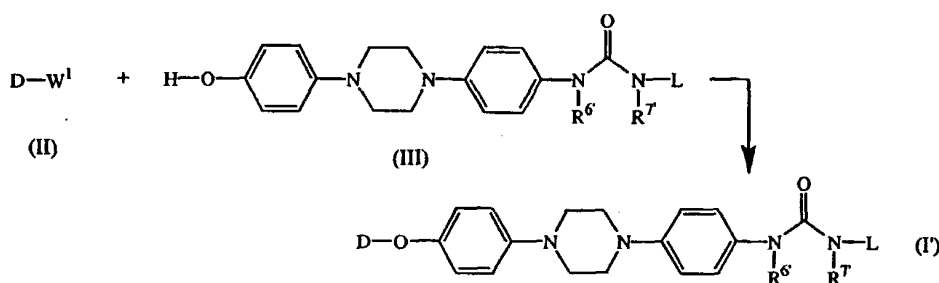
wherein Alk is 2,3-butanediyl, 2,3-pentanediyl or 3,4-pentanediyl;

Z¹ is optionally substituted phenyl or optionally substituted phenylmethyl, isopropyl or *tert*-butyl;

Z² is hydrogen, methyl or hydroxymethyl.

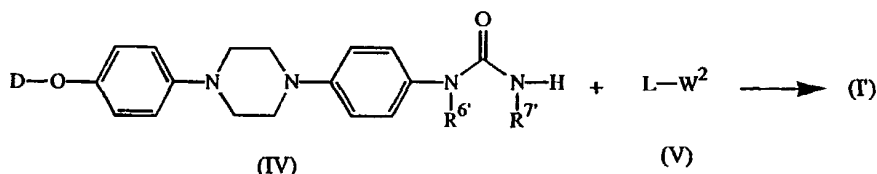
The compounds of the present invention wherein R⁶ and R⁷ are other than hydrogen, said R⁶ and R⁷ being represented by R^{6'} and R^{7'} and said compounds being represented by formula (I'), can be prepared by reacting an intermediate of formula (II) wherein W¹ is a suitable leaving group such as, for example, a halogen, e.g. iodo, an arylsulfonyloxy or an alkanesulfonyloxy group, e.g. *p*-toluenesulfonyloxy, naphthylsulfonyloxy or methanesulfonyloxy, with an intermediate of formula (III) in a reaction-inert solvent such as, for example, *N,N*-dimethylformamide, *N,N*-dimethyl-acetamide, 1-methyl-2-pyrrolidinone, 1,3-dimethyl-2-imidazolidinone, sulfolane or the like, and in the presence of a suitable base such as, for example, sodiumhydroxide or sodiumhydride.

-11-



In this and the following preparations, the reaction products may be isolated from the reaction medium and, if necessary, further purified according to methodologies generally known in the art such as, for example, extraction, crystallization, trituration

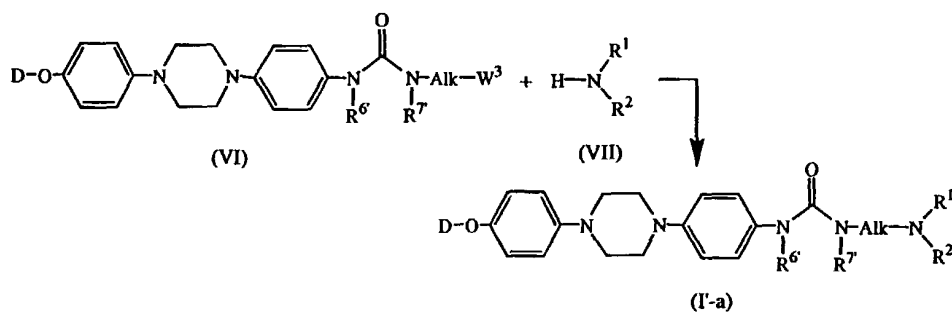
- 5 and chromatography. In particular, stereoisomers can be isolated chromatographically using a chiral stationary phase such as, for example, Chiralpak AD (amylose 3,5 dimethylphenyl carbamate) or Chiralpak AS, both purchased from Daicel Chemical Industries, Ltd, in Japan.
- 10 Compounds of formula (I') may also be prepared by *N*-alkylating an intermediate of formula (IV) with an intermediate of formula (V) wherein W^2 is a suitable leaving group such as, for example, a halogen, and wherein reactive amino groups in L such as primary and secondary amines, in case they are present, are protected with a protective group P such as, for example, a C_{1-4} alkyloxycarbonyl group, in a reaction-inert solvent
- 15 such as, for example, dimethylsulfoxide, in the presence of a base such as, for example, potassium hydroxide. In case L was protected, art-known deprotection techniques can be employed to arrive at compounds of formula (I') after the *N*-alkylation reaction.



- Compounds of formula (I') wherein L is a radical of formula (a), said compounds being represented by formula (I'-a), may be prepared by reacting an intermediate of formula (VI) wherein W^3 is a suitable leaving group such as, for example, a halogen, an arylsulfonyloxy or an alkanesulfonyloxy group, e.g. *p*-toluenesulfonyloxy, naphthylsulfonyloxy or methanesulfonyloxy, with an intermediate of formula (VII) optionally in the presence of a suitable base such as, for example, sodium- or potassium carbonate,
- 20 triethylamine or the like, and optionally in a reaction-inert solvent such as, for example, *N,N*-dimethylformamide, *N,N*-dimethylacetamide, 1-methyl-2-pyrrolidinone, 1,3-dimethyl-2-imidazolidinone, sulfolane or the like. In case R^1 and R^2 form together with the nitrogen atom to which they are attached an azido radical, NaN_3 may be used
- 25

-12-

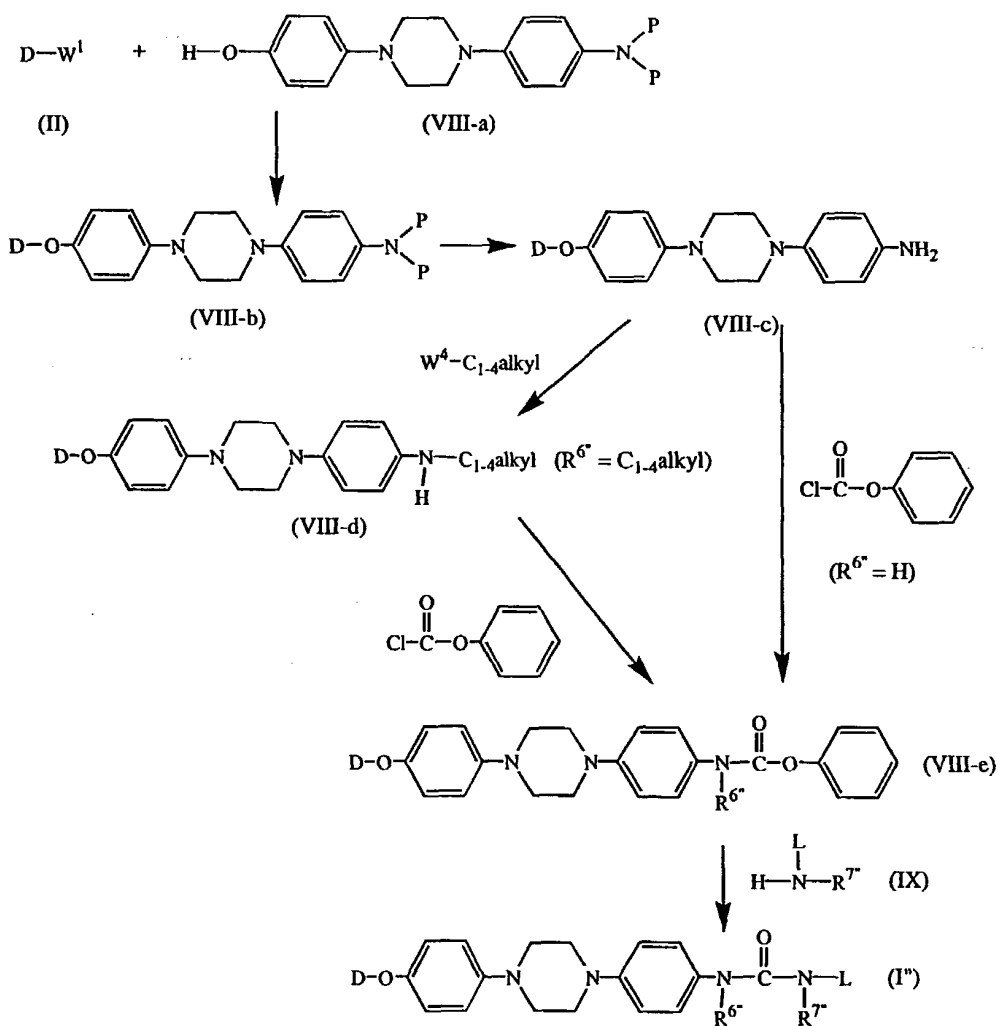
as intermediate of formula (VII).



The compounds of formula (I) wherein at least one of R⁶ or R⁷ is hydrogen, said R⁶ and R⁷ being represented by R^{6'} and R^{7'} and said compounds being represented by formula

5 (I''), can be prepared following the reaction procedure in scheme 1.

Scheme 1



-13-

- In scheme 1, the intermediates of formula (VIII-a) wherein NP_2 is a protected amino group wherein P is for example a C_{1-4} alkyloxycarbonyl group, or a functional derivative of NP_2 such as, for example, a nitro group, are reacted with an intermediate of formula (II) according to the procedure described for the preparation of compounds of formula (I').
- 5 The thus obtained intermediates of formula (VIII-b) may be deprotected according to art-known deprotection techniques, thus obtaining an amine derivative of formula (VIII-c). In case NP_2 is a nitro group, art-known reduction techniques may be used to obtain amines of formula (VIII-c). The amine derivatives of formula (VIII-c) can then be reacted with phenyl chloroformate or a functional derivative thereof. In order to
- 10 obtain compounds of formula (I'') wherein $\text{R}^{6''}$ is C_{1-4} alkyl, amine derivatives of formula (VIII-c) may first be reacted with C_{1-4} alkyl- W^4 wherein W^4 is a suitable leaving group such as, for example, a halogen, and then reacted with phenyl chloroformate. The thus obtained intermediates of formula (VIII-e) may be reacted with an
- intermediate of formula (IX) wherein reactive amino groups in L such as primary and
- 15 secondary amines, in case they are present, are protected with a protective group P such as, for example, a C_{1-4} alkyloxycarbonyl group. Suitably, the reactive amino group may then be deprotected using art-known deprotection techniques to arrive at the desired compound of formula (I').
- 20 The compounds of formula (I) may also be converted into each other following art-known transformations.

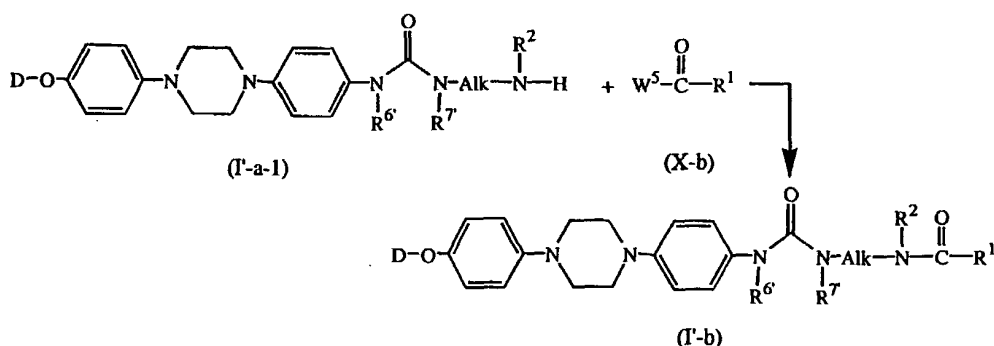
For instance, compounds of formula (I') wherein L is a radical of formula (b), said compounds being represented by formula (I'-b), may be prepared using art-known

25 acylation methods e.g., those described in "Principles of Peptide Synthesis", M. Bodanszky, Springer-Verlag Berlin Heidelberg, 1984.

A particular acylation procedure involves the acylation of a compound of formula (I'-a) wherein R^1 is hydrogen, said compounds being represented by formula (I'-a-1), with an

30 intermediate of formula (X-b) wherein W^5 is a suitable leaving group such as, for example, a halogen or a hydroxy group, in the presence of a suitable base such as, for example, sodiumbicarbonate or *N,N*-dimethylaminopyridine or a functional derivative thereof, and in a reaction-inert solvent such as, for example, dichloromethane, dichloroethane, tetrahydrofuran or the like.

-14-



In case W⁵ is hydroxy, it may be convenient to activate the carboxylic acid of formula (X-b) by adding a diimide such as, for example, *N,N'* dicyclohexylcarbodiimide, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide or a functional derivative thereof.

- Alternatively, the carboxylic acid of formula (X-b) may be activated by adding carbonyldiimidazole or a functional derivative thereof.

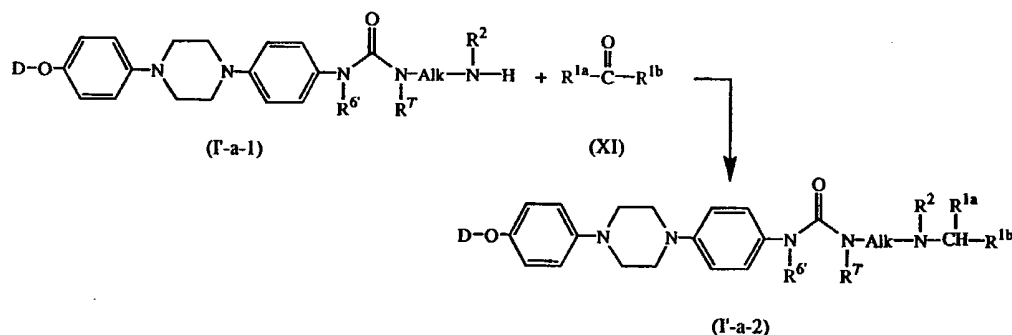
In case an chirally pure intermediate of formula (X-b) is used, fast and enantiomerization-free couplings may be performed by adding hydroxybenzotriazole, benzotriazolyloxytris(dimethylamino) phosphonium hexafluorophosphate, tetrapyrrolidinophosphonium hexafluorophosphate, bromotripyrrolidinophosphonium hexafluorophosphate or a functional derivative thereof (D.Hudson, J. Org. Chem., 1988, 53, p617 & 1999 Novabiochem catalogue & peptide Synthesis Handbook).

- An analogous acylation procedure as for the preparation of compounds of formula (I'-b) may be used for the preparation of compounds of formula (I') wherein L is a radical of formula (c), said compounds being represented by formula (I'-c). In said analogous reaction procedure, the intermediate of formula (X-b) is replaced by a carbonate of formula C₁₋₄alkyl-O-C(=O)-O-R¹ (X-c-1), a chloroformate of formula Cl-C(=O)-O-R¹ (X-c-2) or C₁₋₄alkyl-O-C(=O)-O-C(=O)-O-C₁₋₄alkyl (X-c-3).

- An analogous acylation procedure as for the preparation of compounds of formula (I'-b) may be used for the preparation of compounds of formula (I') wherein L is a radical of formula (d), said compounds being represented by formula (I'-d). In said analogous reaction procedure, the intermediate of formula (X-b) is replaced by an isocyanate of formula O=C=N-R¹ (X-d-1), an isothiocyanate of formula S=C=N-R¹ (X-d-2), a phenylcarbamate of formula *phenyl*-O-C(=O)-NR¹R² (X-d-3), a phenylthiocarbamate of formula *phenyl*-O-C(=S)-NR¹R² (X-d-4), or an intermediate of formula C₁₋₄alkyl-S-C(=NR²)-NR¹R² (X-d-5).

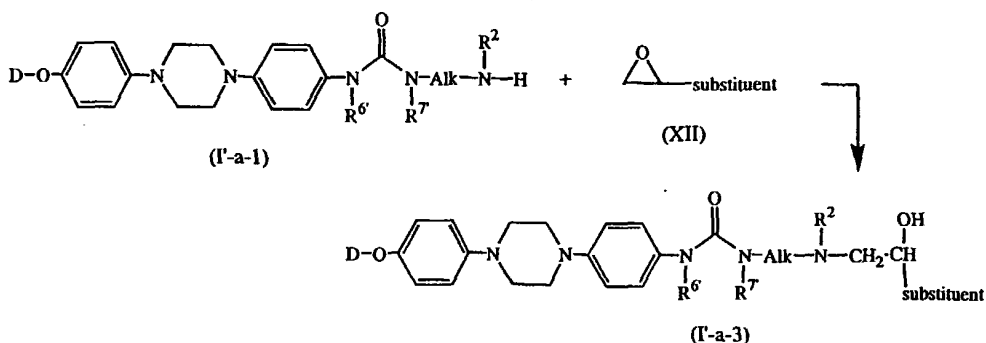
-15-

Compounds of formula (I'-a-1) may also be reductively *N*-alkylated with an aldehyde or keton of formula $R^{1a}C(=O)R^{1b}$ (XI) wherein R^{1a} and R^{1b} are so defined that the radical $-CHR^{1a}R^{1b}$ is encompassed by the definition of R^1 , thus forming compounds of formula (I'-a-2). Said reductive *N*-alkylation may be performed in a reaction-inert solvent such as, for example, toluene, methanol, tetrahydrofuran or a mixture thereof, and in the presence of a reducing agent such as, for example, a borohydride, e.g. sodium borohydride, zinc borohydride, lithium borohydride, sodium cyanoborohydride or triacetoxy borohydride. In case a borohydride is used as a reducing agent, it may be convenient to use a catalyst such as, for example, titanium(IV) isopropoxide as described in J. Org. Chem, 1990, 55, 2552-2554. It may also be convenient to use hydrogen as a reducing agent in combination with a suitable catalyst such as, for example, palladium-on-charcoal or platinum-on-charcoal. The formation of a Schiff base in the first step of the reductive *N*-alkylation can be enhanced by the addition of a suitable reagent to the reaction mixture such as, for example, aluminium *tert*-butoxide, calcium oxide, calcium hydride or a titanium(IV)alkoxide, e.g. titanium(IV)isopropoxide or titanium(IV)-*n*-butoxide. An appropriate catalyst-poison, e.g., thiophene, butanethiol or quinoline-sulphur, may also be added to the reaction mixture to prevent the undesired further hydrogenation of certain functional groups in the reactants and the reaction products. Stirring and optionally elevated temperatures and/or pressure may enhance the rate of the reaction.



Compounds of formula (I') wherein L is a radical of formula (a) and R^1 is $-CH_2-CH(OH)substituent$ wherein the *substituent* belongs to the group of substituents of C_{1-6} alkyl in the definition of R^1 , said compounds being represented by formula (I'-a-3), may be prepared by reacting an intermediate of formula (I'-a-1) with an epoxide of formula (XII) in a reaction-inert solvent such as, for example, 2-propanol.

-16-



Compounds of formula (I) containing a C₁₋₄alkyloxycarbonylamino moiety may be converted to compounds of formula (I) containing the corresponding amino moiety using art-known techniques such as, for example, reaction in dichloromethane and in the presence of trifluoroacetic acid.

Compounds of formula (I') containing a primary amine may be mono-methylated by first protecting the primary amine with a suitable protecting group such as, for example, an arylalkyl group, e.g. benzyl, and subsequently methylating the secondary amine using art-known methylation techniques such as, for example, reaction with paraformaldehyde. The thus obtained tertiary amine may be deprotected using art-known deprotection techniques such as, for example, reaction with hydrogen in tetrahydrofuran or methanol and in the presence of a catalyst such as, for example palladium-on-charcoal, thus obtaining the desired methylated secondary amine.

The compounds of formula (I) may also be converted to the corresponding *N*-oxide forms following art-known procedures for converting a trivalent nitrogen into its *N*-oxide form. Said *N*-oxidation reaction may generally be carried out by reacting the starting material of formula (I) with an appropriate organic or inorganic peroxide.

Appropriate inorganic peroxides comprise, for example, hydrogen peroxide, alkali metal or earth alkaline metal peroxides, e.g. sodium peroxide, potassium peroxide; appropriate organic peroxides may comprise peroxy acids such as, for example, benzenecarboxoperoxy acid or halo substituted benzenecarboxoperoxy acid, e.g. 3-chlorobenzenecarboxoperoxy acid, peroxyalkanoic acids, e.g. peroxyacetic acid, alkylhydroperoxides, e.g. *tert*-butyl hydroperoxide. Suitable solvents are, for example, water, lower alkanols, e.g. ethanol and the like, hydrocarbons, e.g. toluene, ketones, e.g. 2-butanone, halogenated hydrocarbons, e.g. dichloromethane, and mixtures of such solvents.

Some of the intermediates and starting materials used in the above reaction procedures

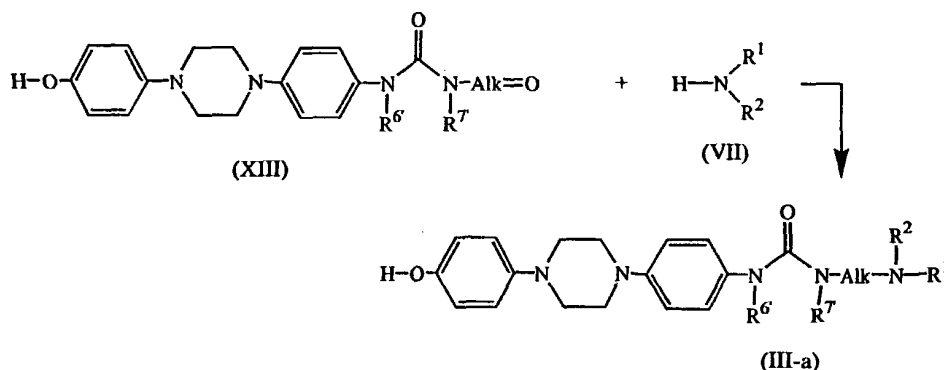
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are commercially available, or may be synthesized according to procedures described elsewhere, e.g. US-4,791,111, US-4,931,444, US-4,267,179, WO95/17407, WO 96/38443, WO 97/00255 and EP-A-0,318,214. Some methods of preparing the intermediates of the present invention are described hereinbelow.

5

For instance, intermediates of formula (III) wherein L is a radical of formula (a), said intermediates being represented by formula (III-a), can be prepared by reductively aminating a carbonyl containing intermediate of formula (XIII) wherein Alk=O is the same as Alk substituted with an oxo group, with an intermediate of formula (VII)

10 following the same reaction procedures as described for the reductive *N*-alkylation of compounds of formula (I'-a-1) with intermediates of formula (XI).



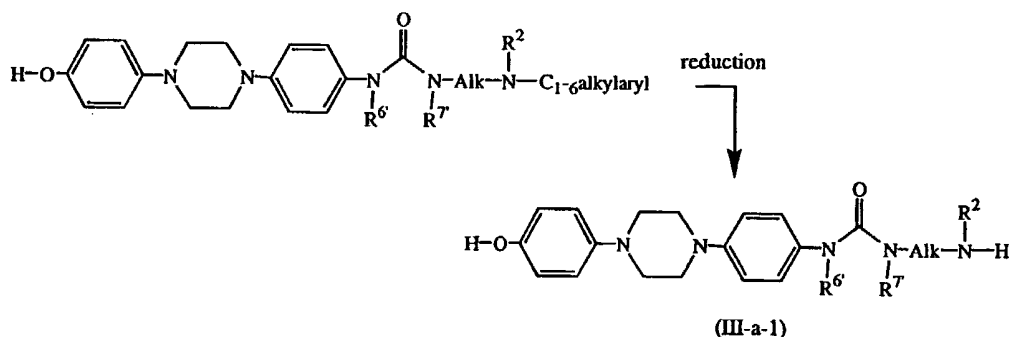
The above reaction procedure may be performed with chirally pure starting materials, employing stereoselective reaction procedures, thus obtaining chirally pure intermediates of formula (III-a). For instance, an stereoselective reductive amination of a chirally pure form of an intermediate of formula (XIII) with a chirally pure form of formula (VII) may be a reaction using hydrogen on palladium-on-charcoal as reducing agent in the presence of a thiophene solution and titanium(IV) isopropoxide. The resulting stereoisomeric forms may be separated using chromatographic or other art-known techniques.

20

It may also be convenient to perform the above reaction on the alkylphenoxy derivatives of the intermediates of formula (XIII).

25 Intermediates of formula (III-a) wherein R¹ is an arylC₁₋₆alkyl group may be reduced using art-known reduction techniques such as, for example, a reduction with hydrogen in the presence of palladium on activated charcoal, thus obtaining intermediates of formula (III-a) wherein R¹ is hydrogen, said intermediates being represented by formula (III-a-1).

-18-



Said intermediates of formula (III-a-1) may be converted to intermediates of formula (III) wherein L is a radical of formula (b), (c) or (d), being represented by formula (III-b), (III-c) and (III-d) respectively, using art-known acylation methods e.g., those described in "Principles of Peptide Synthesis", M. Bodanszky, Springer-Verlag Berlin Heidelberg, 1984 and 1999 Novabiochem Catalogue & Peptide Synthesis Handbook.

Also, amides of formula (III-b) may be hydrolysed using a suitable acid such as, for example hydrochloric acid, thus obtaining intermediates of formula (III-a-1).

Pure stereoisomeric forms of the compounds and the intermediates of this invention may be obtained by the application of art-known procedures. Diastereomers may be separated by physical separation methods such as selective crystallization and chromatographic techniques, e.g. liquid chromatography using chiral stationary phases.

Enantiomers may be separated from each other by the selective crystallization of their diastereomeric salts with optically active acids. Alternatively, enantiomers may be separated by chromatographic techniques using chiral stationary phases. Said pure stereoisomeric forms may also be derived from the corresponding pure stereoisomeric forms of the appropriate starting materials, provided that the reaction occurs stereoselectively or stereospecifically. Preferably if a specific stereoisomer is desired, said compound will be synthesized by stereoselective or stereospecific methods of preparation. These methods will advantageously employ chirally pure starting materials. Stereoisomeric forms of the compounds of formula (I) are obviously intended to be included within the scope of the invention.

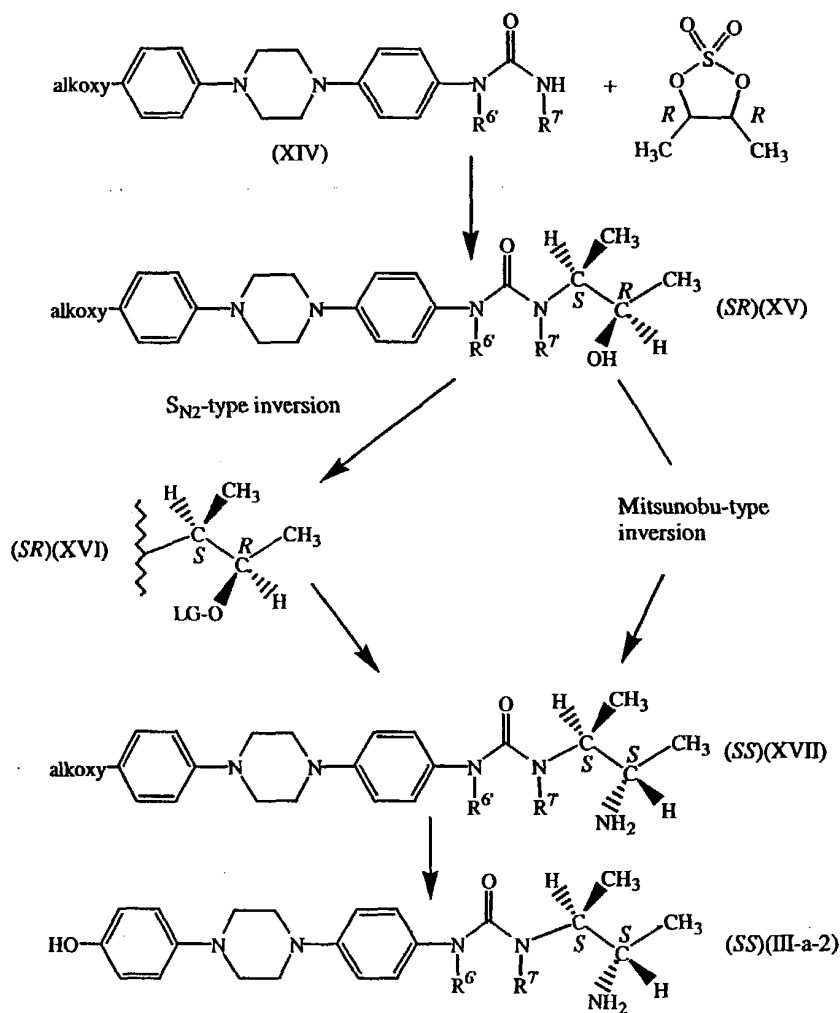
The chirally pure forms of the compounds of formula (I) form a preferred group of compounds. It is therefore that the chirally pure forms of the intermediates of formula (II), (III) and (VI), their *N*-oxide forms and their addition salt forms are particularly useful in the preparation of chirally pure compounds of formula (I). Also enantiomeric mixtures and diastereomeric mixtures of intermediates of formula (II), (III) and (VI) are

-19-

useful in the preparation of compounds of formula (I) with the corresponding configuration. Said chirally pure forms and also the enantiomeric and diastereomeric mixtures of the intermediates of formula (III) are deemed novel.

- 5 A specific way to stereoselectively prepare intermediates of formula (III-a) wherein R^1 and R^2 are hydrogen and Alk is $-\text{CH}(\text{CH}_3)-\text{CH}(\text{CH}_3)-$ wherein both asymmetric carbon atoms have the *S*-configuration, being represented by formula (SS)(III-a-2), or the alkoxyphenyl analogues thereof, is as depicted in scheme 2a.

Scheme 2a



- 10 The reaction of an intermediate of formula (XIV) with (4*R-trans*)-4,5-dimethyl-2,2-dioxido-1,3,2-dioxathiolane may be performed in a suitable solvent, preferably a polar aprotic solvent such as, for example, dimethylacetamide or *N,N*-dimethylformamide,

-20-

and in the presence of a base such as, for example, potassium *tert*-butanolate, potassium hydroxide or potassium hydride. Subsequently, an acid such as, sulfuric acid, may be added to the reaction mixture, thus obtaining an intermediate of formula (SR)(XV) whereby the 2-hydroxy-1-methylpropyl moiety has the erythro form. Then, the carbon atom bearing the alcohol function of said 2-hydroxy-1-methylpropyl moiety is epimerized, preferably 100 % inverted, thus obtaining intermediate (SS)(XVII) whereby the 2-amino-1-methylpropyl moiety has the threo form. Two pathways are convenient.

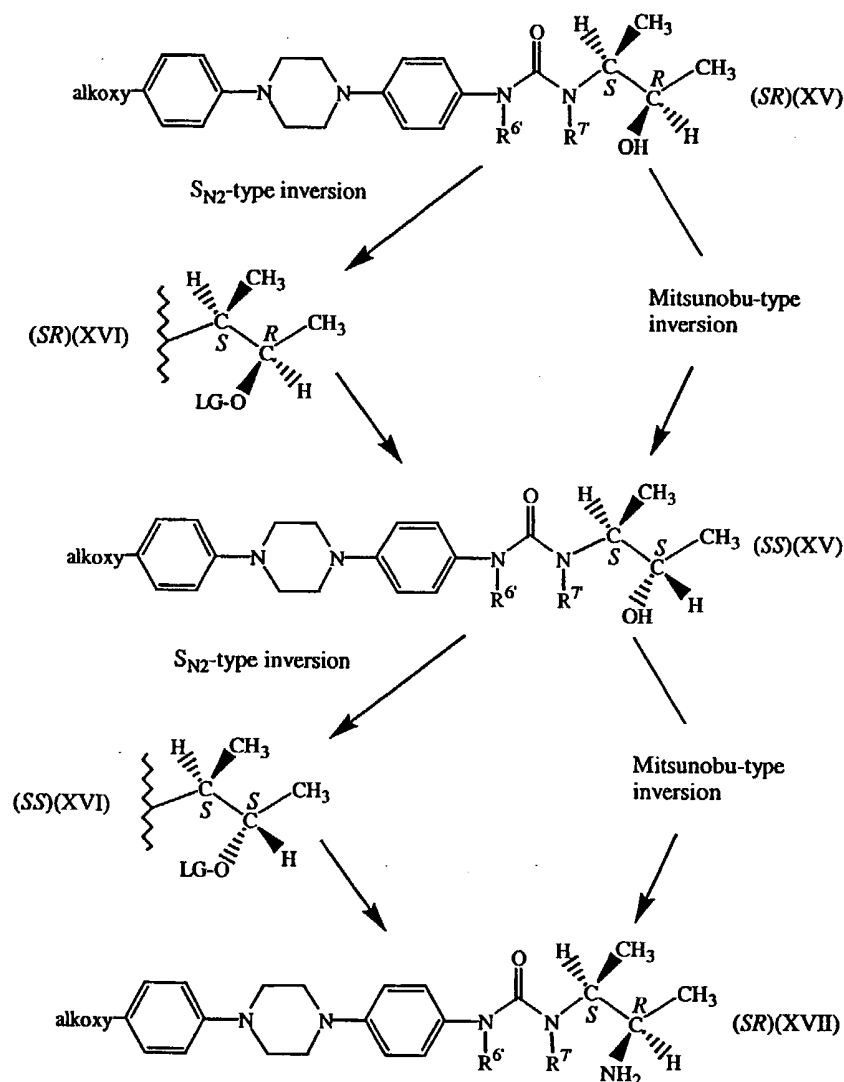
A first pathway involves the transformation of the alcohol function into a suitable leaving group O-LG by, for instance, derivatizing the hydroxy group with an organic acid such as, for example, a sulfonic acid, e.g. *p*-toluenesulfonic acid or methanesulfonic acid; thus obtaining an intermediate of formula (SR)(XVI). The carbon atom bearing the leaving group in said intermediate (SR)(XVI) may subsequently be epimerized, preferably 100 % inverted, by a S_N2-type reaction with a suitable nucleophilic reagent such as, for example, NaN₃, which may subsequently be reduced to the primary amine of formula (SS)(XVII). Alternatively, the Gabriel synthesis, its Ing-Manske modification or another functional modification thereof may be employed to prepare a primary amine of formula (SS)(XVII).

An alternative pathway for inverting the stereochemistry of the carbon atom bearing the alcohol function is the use of the Mitsunobu reaction. The alcohol function of an intermediate of formula (SR)(XV) is activated with diisopropyl azodicarboxylate or a functional derivative thereof such as diethyl azodicarboxylate, in the presence of triphenylphosphine, and in a polar aprotic solvent such as, for example, dimethylacetamide or dimethylformamide. The thus obtained activated alcohol is subsequently reacted with an amide such as, for example, 2,2,2-trifluoroacetamide or a functional derivative thereof. The thus obtained amide whereby the 2-hydroxy-1-methylpropyl moiety has been transformed to the threo form may subsequently be hydrolysed using art-known hydrolysis techniques, thus obtaining an intermediate of formula (SS)(XVII).

In order to obtain intermediates of formula (SR)(XVII), an additional inversion step can be introduced as is depicted in scheme 2b.

-21-

Scheme 2b



The intermediates of formula (SR)(XV) is converted to an intermediate of formula (SS)(XV) using two possible pathways. A first one involves the transformation of the alcohol function into a suitable leaving group O-LG as described hereinabove; thus obtaining an intermediate of formula (SR)(XVI). The carbon atom bearing the leaving group in said intermediate (SR)(XVI) may subsequently be epimerized, preferably 100 % inverted, by a S_N2 -type reaction with a suitable nucleophilic reagent such as, for example, an alcoholate, e.g. a benzyloxy group; an hydroxy salt of an alkali metal, e.g. sodiumhydroxide or potassium hydroxide; an acetate, e.g. sodium acetate. Said reaction is performed in a suitable solvent, preferably a polar aprotic solvent such as, for example, dimethylacetamide, *N*-methylpyrrolidinone, dimethylimidazolidinone or

-22-

sulfolane. In case an alcoholate or an acetate is used in the S_N2 reaction, the thus obtained intermediate may be deprotected using art-known deprotection techniques, thus obtaining an alcohol intermediate of formula (SS)(XV).

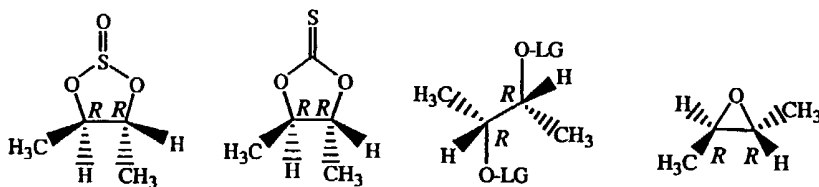
- 5 Another pathway involves the Mitsunobu reaction. The alcohol function of an intermediate of formula (SR)(XV) is activated as described hereinabove. The thus obtained activated alcohol is subsequently reacted with a carboxylic acid such as, for example, 4-nitrobenzoic acid, acetic acid, monochloroacetic acid. The thus obtained ester may subsequently be hydrolysed using art-known hydrolysis techniques, thus
10 obtaining an intermediate of formula (SS)(XV).

The intermediates of formula (SS)(XV) may then be reacted to obtain intermediates of formula (SR)(XVII) using the same reaction pathways as described for the preparation of intermediates (SS)(XVII) starting from (SR)(XV).

15

Finally, the alkoxyphenyl moiety of the intermediates of formula (SS)(XVII) or (SR)(XVII) may be transformed to the phenol moiety using for instance, hydrobromic acid, or a mixture of hydrobromic acid and hydrobromic acid in acetic acid, in the presence of NaHSO_3 , thus obtaining an intermediate of formula (SS)(III-a-2) or
20 (SR)(III-a-2).

Suitable alternatives for (4*R-trans*)-4,5-dimethyl-2,2-dioxide-1,3,2-dioxathiolane include the following chirally pure intermediates :



- 25 wherein LG is a leaving group such as, for example, *p*-toluenesulfonyl.

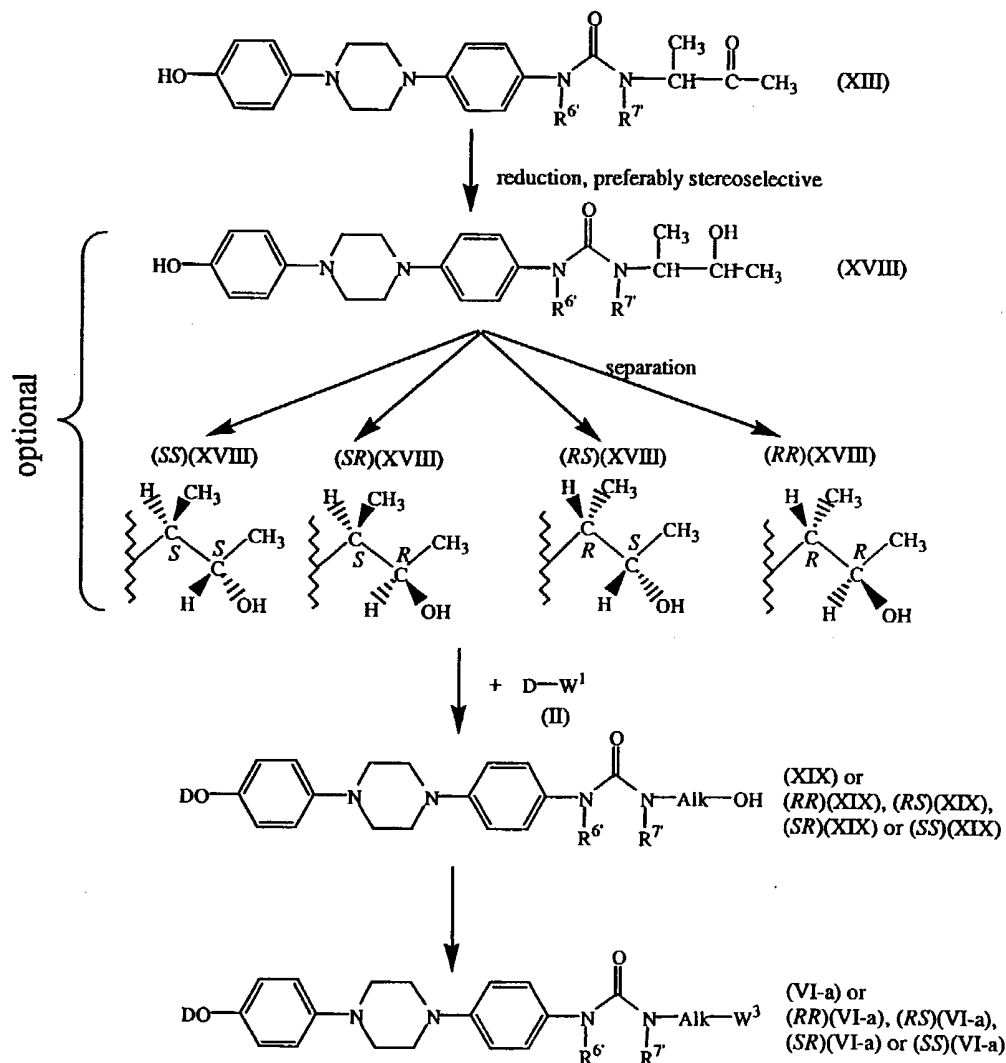
The intermediates of formula (III-a-2), whereby the 2-hydroxy-1-methylpropyl moiety has the [*R*-(*R*^{*},*R*^{*})] form, said intermediates being represented by (RR)(III-a-2), may be prepared using the same reaction pathways as depicted in scheme 2 but replacing (4*R-trans*)-4,5-dimethyl-2,2-dioxide-1,3,2-dioxathiolane with its enantiomer (4*S-trans*)-4,5-dimethyl-2,2-dioxide-1,3,2-dioxathiolane.
30

Intermediates of formula (VI) can be prepared by reducing an intermediate of formula (XIII) and subsequently introducing a leaving group W^3 . In particular, intermediates of

-23-

formula (VI) wherein Alk is $-\text{CH}(\text{CH}_3)-\text{CH}(\text{CH}_3)-$, said intermediates being represented by formula (VI-a), may be prepared according to the reaction scheme as depicted in scheme 3. Optionally, the chirally pure intermediates of formula (VI-a), represented by (SS)(VI-a), (SR)(VI-a), (RS)(VI-a) and (RR)(VI-a), can be prepared using this procedure.

Scheme 3



Suitable stereoselective reduction conditions include the use of K-selectride in a suitable solvent such as, for example, dimethylacetamide or tetrahydrofuran; the use of sodiumborohydride optionally in combination with $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$, ZnCl_2 or $\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$ in a suitable solvent such as, for example, dimethylacetamide, dimethylformamide, methanol or tetrahydrofuran. Said reduction conditions favour the threo form of the

2-hydroxy-1-methylpropyl moiety, *i.e.* the form where the two asymmetric carbon atoms have identical absolute configuration. Recrystallisation of the obtained intermediate of formula (XVIII) after stereoselective reduction may even further improve the ratio threo/erythro in favor of the threo form. The desired stereoisomeric forms of the intermediates of formula (XVIII), being (*RR*)(XVIII), (*SS*)(XVIII), (*RS*)(XVIII) and (*SR*)(XVIII), can then optionally be isolated chromatographically using a chiral stationary phase such as, for example, Chiralpak AD (amylose 3,5 dimethylphenyl carbamate) purchased from Daicel Chemical Industries, Ltd, in Japan. The intermediate of formula (XVIII) or one or more of its stereoisomeric forms, may then be further reacted with an intermediate of formula (II) as described hereinabove for the general preparation of compounds of formula (I'). Finally, the hydroxy group of the thus obtained intermediates of formula (XIX) or a chirally pure form thereof, may be transformed into a suitable leaving group W³ by, for instance, derivatizing the hydroxy group with an organic acid such as, for example, a sulfonic acid, *e.g.* *p*-toluenesulfonic acid or methanesulfonic acid; thus obtaining an intermediate of formula (VI-a) or a chirally pure form thereof.

The compounds of formula (I), the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof are useful agents for combating fungi *in vivo*. The present compounds are broad-spectrum antifungals. They are active against a wide variety of fungi, such as *Candida* spp., *e.g.* *Candida albicans*, *Candida glabrata*, *Candida krusei*, *Candida parapsilosis*, *Candida kefyr*, *Candida tropicalis*; *Aspergillus* spp., *e.g.* *Aspergillus fumigatus*, *Aspergillus niger*, *Aspergillus flavus*; *Cryptococcus neoformans*; *Sporothrix schenckii*; *Fonsecaea* spp.; *Epidermophyton floccosum*; *Microsporum canis*; *Trichophyton* spp.; *Fusarium* spp.; and several dematiaceous hyphomycetes. Of particular interest is the improved activity of some of the present compounds against *Fusarium* spp.

In vitro experiments, including the determination of the fungal susceptibility of the present compounds as described in the pharmacological example hereinafter, indicate that the compounds of formula (I) have a favourable intrinsic inhibitory capacity on fungal growth in for instance *Candida albicans*. Other *in vitro* experiments such as the determination of the effects of the present compounds on the sterol synthesis in, for instance, *Candida albicans*, also demonstrate their antifungal potency. Also *in vivo* experiments in several mouse, guinea-pig and rat models show that, after both oral and intravenous administration, the present compounds are potent antifungals.

An additional advantage of some of the present compounds is that they are not only fungistatic, as most of the known azole antifungals, but are also fungicidal at acceptable therapeutic doses against many fungal isolates.

- 5 The compounds of the present invention are chemically stable and have a good oral availability.

The solubility profile in aqueous solutions of the compounds of formula (I) makes them suitable for intravenous administration. Particularly interesting compounds are those
10 compounds of formula (I) having a water-solubility of at least 0.01 mg/ml at a pH of at least 4, preferably, a water-solubility of at least 0.1 mg/ml at a pH of at least 4, and more preferred a water-solubility of at least 1 mg/ml at a pH of at least 4. Most preferred are those compounds having a water-solubility of 5 mg/ml or higher at a pH of at least 4.

15 In view of the utility of the compounds of formula (I), there is provided a method of treating warm-blooded animals, including humans, suffering from fungal infections. Said method comprises the systemic or topical administration of an effective amount of a compound of formula (I), a *N*-oxide form, a pharmaceutically acceptable addition salt
20 or a possible stereoisomeric form thereof, to warm-blooded animals, including humans. Hence, compounds of formula (I) are provided for use as a medicine, in particular, the use of a compound of formula (I) in the manufacture of a medicament useful in treating fungal infections is provided.

- 25 The present invention also provides compositions for treating or preventing fungal infections comprising a therapeutically effective amount of a compound of formula (I) and a pharmaceutically acceptable carrier or diluent.

In view of their useful pharmacological properties, the subject compounds may be
30 formulated into various pharmaceutical forms for administration purposes. To prepare the pharmaceutical compositions of this invention, a therapeutically effective amount of a particular compound, in base or addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of
35 preparation desired for administration. These pharmaceutical compositions are desirably in unitary dosage form suitable, preferably, for administration orally, rectally, topically, percutaneously, transungually or by parenteral injection. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media

-26-

may be employed, such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs and solutions: or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. As appropriate compositions for topical application there may be cited all compositions usually employed for topically administering drugs e.g. creams, gel, dressings, shampoos, tinctures, pastes, ointments, salves, powders and the like. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not cause a significant deleterious effect to the skin. Said additives may facilitate the administration to the skin and/or may be helpful for preparing the desired compositions. These compositions may be administered in various ways, e.g., as a transdermal patch, as a spot-on, as an ointment.

Transungual compositions are in the form of a solution and the carrier optionally comprises a penetration enhancing agent which favours the penetration of the antifungal into and through the keratinized ungual layer of the nail. The solvent medium comprises water mixed with a co-solvent such as an alcohol having from 2 to 6 carbon atoms, e.g. ethanol.

For parenteral compositions, the carrier will usually comprise sterile water, at least in large part. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution.

Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. For parenteral compositions, other ingredients, to aid solubility for example, e.g. cyclodextrins, may be included.

Appropriate cyclodextrins are α -, β -, γ -cyclodextrins or ethers and mixed ethers thereof wherein one or more of the hydroxy groups of the anhydroglucose units of the cyclodextrin are substituted with C_{1-6} alkyl, particularly methyl, ethyl or isopropyl, e.g. randomly methylated β -CD; hydroxy C_{1-6} alkyl, particularly hydroxyethyl, hydroxypropyl or hydroxybutyl; carboxy C_{1-6} alkyl, particularly carboxymethyl or carboxyethyl; C_{1-6} alkylcarbonyl, particularly acetyl. Especially noteworthy as complexants and/or solubilizers are β -CD, randomly methylated β -CD, 2,6-dimethyl- β -CD, 2-hydroxyethyl- β -CD, 2-hydroxyethyl- γ -CD, 2-hydroxypropyl- γ -CD and (2-carboxymethoxy)propyl- β -CD, and in particular 2-hydroxypropyl- β -CD (2-HP- β -CD).

-27-

The term mixed ether denotes cyclodextrin derivatives wherein at least two cyclodextrin hydroxy groups are etherified with different groups such as, for example, hydroxy-propyl and hydroxyethyl.

- 5 The average molar substitution (M.S.) is used as a measure of the average number of moles of alkoxy units per mole of anhydroglucose. The average substitution degree (D.S.) refers to the average number of substituted hydroxyls per anhydroglucose unit. The M.S. and D.S. value can be determined by various analytical techniques such as nuclear magnetic resonance (NMR), mass spectrometry (MS) and infrared spectroscopy
10 (IR). Depending on the technique used, slightly different values may be obtained for one given cyclodextrin derivative. Preferably, as measured by mass spectrometry, the M.S. ranges from 0.125 to 10 and the D.S. ranges from 0.125 to 3.

- Other suitable compositions for oral or rectal administration comprise particles
15 obtainable by melt-extruding a mixture comprising a compound of formula (I) and an appropriate water-soluble polymer and subsequently milling said melt-extruded mixture. Said particles can then be formulated by conventional techniques into pharmaceutical dosage forms such as tablets and capsules.

- 20 Said particles consist of a solid dispersion comprising a compound of formula (I) and one or more pharmaceutically acceptable water-soluble polymers. The preferred technique for preparing solid dispersions is the melt-extrusion process comprises the following steps :

- a) mixing a compound of formula (I) and an appropriate water-soluble polymer,
25 b) optionally blending additives with the thus obtained mixture,
c) heating the thus obtained blend until one obtains a homogenous melt,
d) forcing the thus obtained melt through one or more nozzles; and
e) cooling the melt till it solidifies.

- 30 The solid dispersion product is milled or ground to particles having a particle size of less than 600 μm , preferably less than 400 μm and most preferably less than 125 μm .

The water-soluble polymers in the particles are polymers that have an apparent viscosity of 1 to 100 mPa.s when dissolved in a 2 % aqueous solution at 20°C solution.

- 35 For example, suitable water-soluble polymers include alkylcelluloses, hydroxyalkylcelluloses, hydroxyalkyl alkylcelluloses, carboxyalkylcelluloses, alkali metal salts of carboxyalkylcelluloses, carboxyalkylalkylcelluloses, carboxyalkylcellulose esters, starches, pectines, chitin derivatives, polysaccharides,

-28-

polyacrylic acids and the salts thereof, polymethacrylic acids and the salts thereof, methacrylate copolymers, polyvinylalcohol, polyvinylpyrrolidone, copolymers of polyvinylpyrrolidone with vinyl acetate, polyalkylene oxides and copolymers of ethylene oxide and propylene oxide. Preferred water-soluble polymers are hydroxypropyl methylcelluloses.

Also one or more cyclodextrins can be used as water soluble polymer in the preparation of the above-mentioned particles as is disclosed in WO 97/18839. Said cyclodextrins include the pharmaceutically acceptable unsubstituted and substituted cyclodextrins known in the art, more particularly α , β or γ cyclodextrins or the pharmaceutically acceptable derivatives thereof.

Substituted cyclodextrins which can be used include polyethers described in U.S. Patent 3,459,731. Further substituted cyclodextrins are ethers wherein the hydrogen of one or more cyclodextrin hydroxy groups is replaced by C₁₋₆alkyl, hydroxyC₁₋₆alkyl, carboxy-C₁₋₆alkyl or C₁₋₆alkyloxycarbonylC₁₋₆alkyl or mixed ethers thereof. In particular such substituted cyclodextrins are ethers wherein the hydrogen of one or more cyclodextrin hydroxy groups is replaced by C₁₋₃alkyl, hydroxyC₂₋₄alkyl or carboxyC₁₋₂alkyl or more in particular by methyl, ethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, carboxy-methyl or carboxyethyl.

Of particular utility are the β -cyclodextrin ethers, e.g. dimethyl- β -cyclodextrin as described in Drugs of the Future, Vol. 9, No. 8, p. 577-578 by M. Nogradi (1984) and polyethers, e.g. hydroxypropyl β -cyclodextrin and hydroxyethyl β -cyclodextrin, being examples. Such an alkyl ether may be a methyl ether with a degree of substitution of about 0.125 to 3, e.g. about 0.3 to 2. Such a hydroxypropyl cyclodextrin may for example be formed from the reaction between β -cyclodextrin and propylene oxide and may have a MS value of about 0.125 to 10, e.g. about 0.3 to 3.

A more novel type of substituted cyclodextrins is sulfobutylcyclodextrines.

The ratio of active ingredient over cyclodextrin may vary widely. For example ratios of 1/100 to 100/1 may be applied. Interesting ratios of active ingredient over cyclodextrin range from about 1/10 to 10/1. More interesting ratios of active ingredient over cyclodextrin range from about 1/5 to 5/1.

It may further be convenient to formulate the present azole antifungals in the form of nanoparticles which have a surface modifier adsorbed on the surface thereof in an

-29-

amount sufficient to maintain an effective average particle size of less than 1000 nm. Useful surface modifiers are believed to include those which physically adhere to the surface of the antifungal agent but do not chemically bond to the antifungal agent.

- 5 Suitable surface modifiers can preferably be selected from known organic and inorganic pharmaceutical excipients. Such excipients include various polymers, low molecular weight oligomers, natural products and surfactants. Preferred surface modifiers include nonionic and anionic surfactants.
- 10 Yet another interesting way of formulating the present compounds involves a pharmaceutical composition whereby the present antifungals are incorporated in hydrophilic polymers and applying this mixture as a coat film over many small beads, thus yielding a composition which can conveniently be manufactured and which is suitable for preparing pharmaceutical dosage forms for oral administration.
- 15 Said beads comprise a central, rounded or spherical core, a coating film of a hydrophilic polymer and an antifungal agent and a seal-coating polymer layer.

- Materials suitable for use as cores in the beads are manifold, provided that said
- 20 materials are pharmaceutically acceptable and have appropriate dimensions and firmness. Examples of such materials are polymers, inorganic substances, organic substances, and saccharides and derivatives thereof.

- The pharmaceutical compositions mentioned above may also contain a fungicidally
- 25 effective amount of other antifungal compounds such as cell wall active compounds. The term "cell wall active compound", as used herein, means any compound which interferes with the fungal cell wall and includes, but is not limited to, compounds such as papulacandins, echinocandins, and aculeacins as well as fungal cell wall inhibitors such as nikkomycins, e.g. nikkomycin K and others which are described in
- 30 US-5,006,513.

- It is especially advantageous to formulate the aforementioned pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used in the specification and claims herein refers to physically
- 35 discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such dosage unit forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers,

-30-

injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.

- Those of skill in treating warm-blooded animals suffering from diseases caused by fungi could easily determine the therapeutically effective daily amount from the test results given herein. In general, it is contemplated that a therapeutically effective daily amount would be from 0.05 mg/kg to 20 mg/kg body weight.

Experimental part

- Hereinafter, "DMF" is defined as *N,N*-dimethylformamide, "THF" is defined as tetrahydrofuran and "DIPE" is defined as diisopropylether.

A. Preparation of the intermediates

Example A1

- a) A mixture of (\pm)-2,4-dihydro-4-[4-[4-(4-hydroxyphenyl)-1-piperazinyl]phenyl]-2-(1-methyl-2-oxopropyl)-3*H*-1,2,4-triazol-3-one (0.05 mol) (prepared as described in EP-A-0,228,125 and (+)-(*R*)- α -methylbenzenemethanamine (0.1 mol) in THF (500ml) was hydrogenated at 50°C for 48 hours with Pd/C 10% (10g) as a catalyst in the presence of titanium(IV) *n*-butoxide (28.4g) and thiophene solution (10ml). The catalyst was filtered off. Pd/C 10% (10g) was added again. Hydrogenation was continued at 50°C for 48 hours. After uptake of H₂, the mixture was cooled, then the catalyst was filtered off and the filtrate was evaporated. The residue was stirred in CH₂Cl₂ (500ml) and H₂O (50ml) was added. The mixture was acidified with a concentrated HCl solution, alkalized with a concentrated NH₄OH solution and filtered over dicalite. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was triturated in DIPE, filtered off and dried, yielding 23.5g (91%) of [(*R**,*R**)(*R*)+(*R**,*S**)(*R*)]-2,4-dihydro-4-[4-[4-(4-hydroxyphenyl)-1-piperazinyl]phenyl]-2-[2-[(1-phenylethyl)amino]-1-methylpropyl]-3*H*-1,2,4-triazol-3-one (interm. 1).
- b) A mixture of intermediate (1) (0.0457 mol) in THF (400ml) was hydrogenated at 50°C with Pd/C 10% (5g) as a catalyst. After uptake of H₂, H₂O and CH₂Cl₂ were added, then the catalyst was filtered off and the filtrate was evaporated. The residue was triturated in CH₂Cl₂, filtered off and dried, yielding 14g (75%) of (\pm)-[(*R**,*R**)+(*R**,*S**)]-2-(2-amino-1-methylpropyl)-2,4-dihydro-4-[4-[4-(4-hydroxyphenyl)-1-piperazinyl]phenyl]-3*H*-1,2,4-triazol-3-one (interm. 2).
- b) A mixture of intermediate (2) (0.025 mol) and acetic anhydride (0.03 mol) in CH₂Cl₂ (300ml) was stirred at room temperature. A mixture of NaHCO₃ (5g) in H₂O (100ml) was added. The mixture was stirred for 2 hours and CH₃OH was added. The organic

-31-

layer was separated, dried, filtered and the solvent was evaporated. The residue was purified by HPLC over silica gel (eluent: CH₂Cl₂/CH₃OH 97/3 to 90/10). Two pure fractions were collected and their solvents were evaporated.

5 A first fraction was separated into its enantiomers by column chromatography (eluent: ethanol/2-propanol 50/50; column: CHIRALPAK AS). Two pure fractions were collected and their solvents were evaporated. The residue was triturated in 2-propanol, filtered off and dried, yielding 0.37g (3.2%) of *[R(R*,R*)]-N-[2-[4,5-dihydro-4-[4-[4-(4-hydroxyphenyl)-1-piperazinyl]phenyl]-5-oxo-1H-1,2,4-triazol-1-yl]-1-methylpropyl]acetamide* (interm. 3a) and 2.81g (25%) *[S(R*,R*)]-N-[2-[4,5-dihydro-4-[4-[4-(4-hydroxyphenyl)-1-piperazinyl]phenyl]-5-oxo-1H-1,2,4-triazol-1-yl]-1-methylpropyl]acetamide* (interm. 3b).

The second fraction was separated into its enantiomers by column chromatography (eluent: hexane / 2-propanol / CH₃OH 30/55/15; column: CHIRALPAK AD). Two pure fractions were collected and their solvents were evaporated. The residue was
15 triturated in 2-propanol, filtered off and dried, yielding 0.47 g (4%) of *[S(R*,S*)]-N-[2-[4,5-dihydro-4-[4-[4-(4-hydroxyphenyl)-1-piperazinyl]phenyl]-5-oxo-1H-1,2,4-triazol-1-yl]-1-methylpropyl]acetamide* (interm. 3c) and 3.21g (28%) of *[R(R*,S*)]-N-[2-[4,5-dihydro-4-[4-[4-(4-hydroxyphenyl)-1-piperazinyl]phenyl]-5-oxo-1H-1,2,4-triazol-1-yl]-1-methylpropyl]acetamide* (interm. 3d; mp. 264.3°C); $[\alpha]_{20}^D = +10.96^\circ$ @ 20.07
20 mg/2ml in DMF).

c) A mixture of intermediate (3d) (0.0069 mol) in HCl conc. (50ml) was stirred and refluxed for 48 hours. The solvent was evaporated and the residue was dissolved in H₂O (50ml). The mixture was alkalized with NH₄OH and extracted with CH₂Cl₂/CH₃OH 80/20 (500ml). The organic layer was separated, dried, filtered and the solvent
25 was evaporated. The residue was triturated in 2-propanol, filtered off and dried, yielding 2.6g (92%) of *[R(R*,S*)]-2-(2-amino-1-methylpropyl)-2,4-dihydro-4-[4-[4-(4-hydroxyphenyl)-1-piperazinyl]phenyl]-3H-1,2,4-triazol-3-one* (interm. 4; mp. 237.2°C; $[\alpha]_{20}^D = +1.01^\circ$ @ 19.79 mg/2ml in DMF).

d) A mixture of intermediate 4 (0.042 mol) and benzaldehyde (0.042 mol) in THF
30 (500ml) was hydrogenated at 50°C with palladium on activated carbon 10% (2g) as a catalyst in the presence of a 4% thiophene solution (1ml). After uptake of hydrogen (1 equiv), the catalyst was filtered off and the filtrate was evaporated. The residue was purified by column chromatography over silica gel (eluent 1: CH₂Cl₂/CH₃OH 98/2, eluent 2: CH₂Cl₂/(CH₃OH/NH₃) 95/5). The desired fraction was collected and the
35 solvent was evaporated. The residue was triturated in 2-propanol, filtered off and dried, yielding 15g (71%) of *[R-(R*,S*)]-2,4-dihydro-4-[4-[4-(4-hydroxyphenyl)-1-piperazinyl]phenyl]-2-[1-methyl-2-[(phenylmethyl)amino]propyl]-3H-1, 2,4-triazin-3-*

one (interm. 5).

Example A2

[(R*,R*)(S)+(R*,S*)(S)]-2,4-dihydro-4-[4-[4-(4-hydroxyphenyl)-1-piperazinyl]phenyl]-2-[2-[(1-phenylethyl)amino]-1-methylpropyl]-3H-1,2,4-triazol-3-one (interm. 6) (0.51 mol) which was prepared analogous to intermediate 1, was separated into its isomers by HPLC over silica gel (eluent 1: CH₂Cl₂/2-propanol 95/5 to 90/10, eluent 2: CH₂Cl₂/CH₃OH 90/10). Two desired fractions were collected and their solvents were evaporated.

A first fraction was triturated in CH₃CN, filtered off and dissolved in CH₂Cl₂. The mixture was extracted with a diluted HCl solution and separated into its layers. The aqueous layer was neutralized with NaHCO₃ and extracted with CH₂Cl₂. The combined organic layer was dried, filtered and the solvent was evaporated. The residue was triturated in CH₃CN, filtered off and dried, yielding 54.4g of [S(R*,R*)(R*)]-2,4-dihydro-4-[4-[4-(4-hydroxyphenyl)-1-piperazinyl]phenyl]-2-[1-methyl-2-[(1-phenylethyl)amino]propyl]-3H-1,2,4-triazol-3-one (interm. 7a).

The second fraction was stirred in CH₃CN. The precipitate was filtered off and dried, yielding 9.5g of [R(R*,S*)(S*)]-2,4-dihydro-4-[4-[4-(4-hydroxyphenyl)-1-piperazinyl]phenyl]-2-[1-methyl-2-[(1-phenylethyl)amino]propyl]-3H-1,2,4-triazol-3-one monohydrochloride (interm. 7b).

Example A3

a) A mixture of 2,5-anhydro-1,3,4-trideoxy-2-C-(2,4-difluorophenyl)-4-(hydroxymethyl)-1-(1H-1,2,4-triazol-1-yl)-pentitol, (0.044 mol) (prepared according to the procedure described in WO 89/04829) and 4-dimethylamino-pyridine (0.5g) in triethylamine (16ml) and CH₂Cl₂ (75ml) was stirred at room temperature.

2-Naphthalenesulfonyl chloride (0.05 mol) was added under N₂ and the mixture was stirred overnight. The mixture was poured into water and extracted with CH₂Cl₂. The organic layer was evaporated and the residue was purified by column chromatography over silica gel (eluent : ethylacetate/hexane/CH₂Cl₂ 1/1/2). The desired fractions were collected and evaporated, yielding 6g (±)-*cis*-[5-(2,4-difluorophenyl)tetrahydro-5-(1H-1,2,4-triazol-1-ylmethyl)-3-furanyl]methyl 2-naphthalenesulfonate (interm. 8a) and a second residue. A sample (1.1g) of the second residue was triturated in 2-propanol, yielding 1g (±)-*trans*-[5-(2,4-difluorophenyl)tetrahydro-5-(1H-1,2,4-triazol-1-ylmethyl)-3-furanyl]methyl 2-naphthalenesulfonate (interm. 8b). Intermediate 8a (0.015 mol) was separated into two enantiomers by chiral column chromatography over AD-phase (eluent: 100% ethanol). Two pure fraction groups were collected and their organic solvent was evaporated to give 3.8 g of residue I and 4.1 g of residue II.

-33-

Residue I was stirred in DIPE (50 ml), filtered off and dried, yielding 3.45 g (2*S*-*cis*)-[5-(2,4-difluorophenyl)tetrahydro-5-(1*H*-1,2,4-triazol-1-ylmethyl)-3-furanyl]methyl 2-naphthalenesulfonate (interm. 9a). Residue (II) was stirred in DIPE (50 ml), filtered off and dried, yielding 3.54 g (2*R*-*cis*)-[5-(2,4-difluorophenyl)tetrahydro-5-(1*H*-1,2,4-triazol-1-ylmethyl)-3-furanyl]methyl 2-naphthalenesulfonate (interm. 9b).

Example A4

a) Reaction under N₂ atmosphere. A mixture of (±)-2,4-dihydro-4-[4-[4-(4-hydroxyphenyl)-1-piperazinyl]phenyl]-2-(1-methyl-2-oxopropyl)-3*H*-1,2,4-triazol-3-one (0.590 mol) in CH₂Cl₂ (6000 ml) with triethylamine (60 g) was stirred for 30 min. S-valine ethyl ester hydrochloride (0.3165 mol) was added. Sodium tris(acetato-*O*)hydroborate (I-) (0.3185 mol) was added and the mixture was stirred for 2 hours at room temperature. More S-valine ethyl ester hydrochloride (0.3165 mol) and sodium tris(acetato-*O*)hydroborate (I-) (0.3185 mol) were added and the reaction mixture was stirred overnight at room temperature. More S-valine ethyl ester hydrochloride (13 g) and sodium tris(acetato-*O*)hydroborate (I-) (28 g) were added portionwise over one hour and the resulting reaction mixture was stirred overnight at room temperature. Water (2 L) was added. The reaction mixture was stirred for 2 hours. The organic layer was separated, washed with water, dried, filtered and the solvent was evaporated. The residue was stirred in DIPE, filtered off and dried, yielding 315 g ethyl [A(S)]-*N*-[2-[4,5-dihydro-4-[4-[4-(4-hydroxyphenyl)-1-piperazinyl]phenyl]-1*H*-1,2,4-triazol-1-yl]-1-methylpropyl]valine (interm. 10).

b) Reaction under N₂ atmosphere. A mixture of intermediate 10 (0.745 mol) in THF (3000 ml) was stirred for one hour at 40 °C. The mixture was allowed to cool to 30 °C. 2M LiBH₄ in THF (0.800 mol) was added dropwise over one hour at 30 °C. After addition of 100 ml, the reaction mixture was gradually warmed to 60 °C while the rest of LiBH₄ was added dropwise. Then, the reaction mixture was stirred and refluxed for about 60 hours. The reaction mixture was cooled. 2-Propanone (500 ml) was added dropwise over 2 hours. Water (800 ml) was added over 1.5 hours. More water (2 L) was added. A solution of NH₄Cl (350 g) in water (1.5 L) was added and the mixture was stirred for 2 hours. The layers were separated. The organic layer was dried, filtered and the solvent was evaporated. The residue was stirred in DIPE, filtered off and dried. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 95/5). The desired fractions were collected and the solvent was evaporated, yielding 120 g (32.6%) of [B(S)]-2,4-dihydro-2-[2-[1-(hydroxymethyl)-2-methylpropyl]amino]-1-methylpropyl]-4-[4-[4-(4-hydroxyphenyl)-1-piperazinyl]phenyl]-3*H*-1,2,4-triazol-3-one (intermediate 11).

Example A5

- a) A mixture of 2,4-dihydro-4-[4-[4-(4-methoxyphenyl)-1-piperazinyl]phenyl]-3H-1,2,4-triazol-3-one (0.05 mol) prepared as described in EP-A-0,006,711, 3-bromo-2-pentanone (0.073 mol) and K₂CO₃ (10g) in DMF (200ml) and toluene (200ml) was stirred and refluxed overnight using a water separator. The solvent was evaporated. The residue was dissolved in CH₂Cl₂. The organic solution was washed, dried, filtered and the solvent was evaporated. The residue was crystallized from 2-propanol. The precipitate was filtered off and the filtrate was evaporated. The residue was triturated in DIPE, filtered off and dried, yielding 4.6g of (±)-2-(1-ethyl-2-oxopropyl)-2,4-dihydro-4-[4-[4-(4-methoxyphenyl)-1-piperazinyl]phenyl]-3H-1,2,4-triazol-3-one (interm. 12).
- b) A mixture of NaHSO₃ (0.5g) in HBr 48 % (50ml) was stirred for 15 min. Intermediate 12 (0.01 mol) was added. The mixture was stirred and refluxed for 2 hours. The solvent was evaporated. The residue was dissolved in H₂O. The solution was neutralized with Na₂CO₃ and extracted with CH₂Cl₂. The organic layer was separated, washed, dried, filtered and the solvent was evaporated. The residue was triturated in DIPE, filtered off and dried, yielding 2.7g (64%) of (±)-2-(1-ethyl-2-oxopropyl)-2,4-dihydro-4-[4-[4-(4-hydroxyphenyl)-1-piperazinyl]phenyl]-3H-1,2,4-triazol-3-one (interm. 13).
- c) A mixture of intermediate 13 (0.016 mol), benzenemethanamine (0.028 mol) and Pd/C 10 % (2g) in a 4% thiophene solution (2ml) and THF (300ml) was stirred at 140°C under a 100 atm pressure for 16 hours, then cooled and filtered. The filtrate was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 98/2). The pure fractions were collected and the solvent was evaporated. The residue was triturated in DIPE and 2-propanol, filtered off and dried. The residue was separated by HPLC over C 18 (eluent: (ammonium acetate 0.5% in H₂O/CH₃CN 90/10)/CH₃OH 40/60, 0/100 and 40/60). The desired fraction was collected and the solvent was evaporated. The residue was purified again by HPLC over silica gel (eluent: CH₂Cl₂/hexane/CH₃OH/ethylacetate 40/42/8/10). The desired fraction was collected and the solvent was evaporated, yielding 1.3g of (B)-2-[1-ethyl-2-[(phenylmethyl)amino]propyl]-2,4-dihydro-4-[4-[4-(4-hydroxyphenyl)-1-piperazinyl]phenyl]-3H-1,2,4-triazol-3-one (interm. 14).

B. Preparation of the final compoundsExample B1

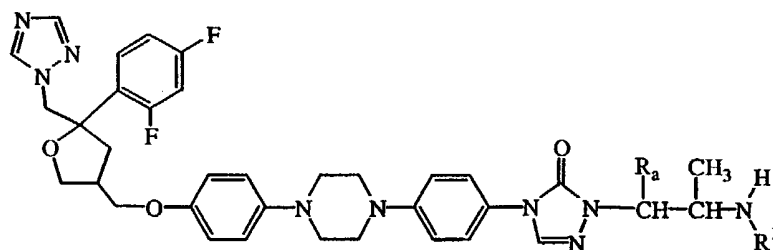
- A mixture of intermediate 9b (0.0026 mol), intermediate 14 (0.0025 mol) and NaOH (0.0078 mol) in DMF (50ml) was stirred at 80°C under N₂ flow for 4 hours and then at room temperature for 48 hours, poured out into H₂O and stirred for 30 min. The

-35-

precipitate was filtered off and dissolved in CH_2Cl_2 . The organic solution was dried, filtered and the solvent was evaporated. The residue was triturated in 2-propanol, filtered off and dried, yielding 1.27g (63.5%) of [2R-[2 α ,4 α (B)]]-4-[4-[4-[5-(2,4-difluorophenyl)tetrahydro-5-(1H-1,2,4-triazol-1-ylmethyl)-3-furonyl]methoxy]phenyl]-1-piperazinyl]phenyl]-2-[1-ethyl-2-[(phenylmethyl)amino]propyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (comp. 4).

Table 1 lists the compounds of formula (I) which were prepared analogous to the procedure described in example B1.

10 Table 1



Comp. No	R _a	R ¹	stereochemistry	optical rotation as $[\alpha]_{20}^D$ @ concentration (in mg/5ml DMF); salts and melting point (in °C)
1	CH ₃	-CH ₂ -phenyl	[2R-[2 α ,4 α (R*,S*)]]	+13.09 @ 25.21; mp 170
2	CH ₃	-CH(CH ₃)-phenyl	[2R-[2 α ,4 α [(R*,S*)(S*)]]]	-21.91 @ 24.87; mp 164
3	CH ₃	$\begin{array}{c} \text{CH}_2\text{OH} \\ \\ \text{---CH---CH---} \\ \quad \quad \\ \text{CH}_3 \quad \text{CH}_3 \end{array}$	[2R-[2 α ,4 α [(S*,R*)(S*)]]]	-45.19 @ 25.45; mp 135
4	C ₂ H ₅	-CH ₂ -phenyl	[2R-[2 α ,4 α (B)]]	-

C. Pharmacological examples

Example C1

A panel of 24 *Candida* isolates, 8 isolates of *Aspergillus* spp., 10 Zygomycetes, 10 *Fusarium* spp., 2 *Cryptococcus neoformans* and 8 dematiaceous hyphomycetes was used.

A series of solutions of the test compounds in dimethyl sulfoxide (DMSO) was prepared. The DMSO solutions were then diluted 100-fold into RPMI 1640 buffered with MOPS, with 2% glucose (Odds, F.C., Antimicrobial Agents and Chemotherapy, 1995, 39, 2051-2060) and inoculated with yeast cells to an initial concentration of 10^4 /ml and with other fungi to an equivalent concentration determined by turbidimetry. Test compounds were added to the medium from DMSO solutions to give final

-36-

- concentrations in the series 10, 3.2, 1.0, 0.32, 0.10, 0.032, 0.010, 0.0032 and 0.0010 μM . Cultures were incubated in the wells of microdilution plates at 37°C for 48 hours for yeasts or at other times and temperatures for other fungi. Once the microdilution plates had been read for growth turbidity spectrophotometrically, samples of material
- 5 were removed from the test cultures to inoculate 10 μl volumes on plates of Sabouraud glucose agar. The plates were incubated at 37°C for 48 hours for yeasts or at other times and temperatures for other species. Table 2 lists for each of the tested species the geometric mean minimum fungicidal concentrations in μM which were determined as
- 10 the lowest concentrations of the test compound that completely or substantially eliminated reappearance of fungal growth on the Sabouraud plates.

Table 2

Comp. No.	<i>Candida</i> spp.	<i>Aspergillus</i> spp.	<i>Zygomycetes</i>	<i>Fusarium</i> spp.	other fungi
1	2.3	0.87	7.5	> 10	2.7
2	1.9	1.0	3.2	> 10	2.7

D. Physicochemical exampleExample D1 : water solubility

- An excess of compound was added to water buffered with 0.1 M citric acid and 0.2 M
- 15 Na_2HPO_4 in a ratio of 61.5/38.5 (pH = 4). The mixture was shaken during 1 day at room temperature. The precipitate was filtered off. The concentration of the compound was measured via UV spectroscopy and is shown in Table 3.

Table 3

Comp. No.	solubility in mg/ml (pH 4)
1	0.036
2	0.02
3	0.14

E. Composition example

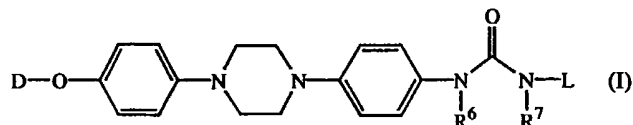
- 20 Example E.1 : Injectable solution.

- 1.8 Grams methyl 4-hydroxybenzoate and 0.2 grams sodium hydroxide were dissolved in about 0.5 l of boiling water for injection. After cooling to about 50°C there were added while stirring 0.05 grams propylene glycol and 4 grams of the active ingredient. The solution was cooled to room temperature and supplemented with water for
- 25 injection q.s. ad 1 l, giving a solution comprising 4 mg/ml of active ingredient. The solution was sterilized by filtration and filled in sterile containers.

-37-

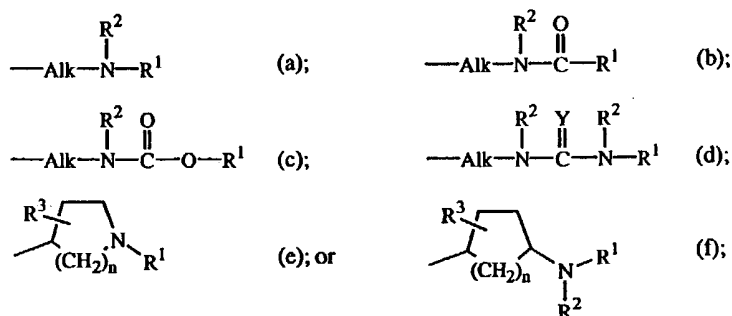
Claims

1. A compound of formula

a *N*-oxide form, a pharmaceutically acceptable addition salt or a stereochemically

5 isomeric form thereof, wherein

L represents a radical of formula

wherein each Alk independently represents C₁₋₆alkanediyl optionally substituted with hydroxy or C₁₋₄alkyloxy;

10 each n independently is 1, 2 or 3;

Y represents O, S or NR²;

each R¹ independently represents aryl, Het¹, or C₁₋₆alkyl optionally substituted with one, two or three substituents each independently selected from halo, hydroxy, mercapto, C₁₋₄alkyloxy, C₁₋₄alkylthio, aryloxy, arylthio, aryl-

15 C₁₋₄alkyloxy, arylC₁₋₄alkylthio, cyano, amino, mono- or di(C₁₋₄alkyl)amino, mono- or di(aryl)amino, mono- or di(arylC₁₋₄alkyl)amino, C₁₋₄alkyloxy-carbonylamino, benzyloxycarbonylamino, aminocarbonyl, carboxyl, C₁₋₄alkyloxycarbonyl, guanidiny, aryl or Het²;

each R² independently represents hydrogen; or

20 in case R¹ and R² are attached to the same nitrogen atom, they may be taken together to form a heterocyclic radical selected from morpholinyl, pyrrolidinyl, piperidinyl, homopiperidinyl or piperazinyl; said heterocyclic radical may optionally be substituted with C₁₋₄alkyl, aryl, Het², arylC₁₋₄alkyl, Het²C₁₋₄alkyl, hydroxyC₁₋₄alkyl, amino, mono- or di(C₁₋₄alkyl)amino, aminoC₁₋₄alkyl, mono- or di(C₁₋₄alkyl)aminoC₁₋₄alkyl, carboxyl, aminocarbonyl, C₁₋₄alkyloxycarbonyl, C₁₋₄alkyloxycarbonylamino or mono- or di(C₁₋₄alkyl)aminocarbonyl; or

25

they may be taken together to form an azido radical;

each R^3 independently represents hydrogen, hydroxy or C_{1-4} alkyloxy;

aryl represents phenyl, naphthalenyl, 1,2,3,4-tetrahydro-naphthalenyl, indenyl or indanyl; each of said aryl groups may optionally be substituted with one or more substituents selected from halo, C_{1-4} alkyl, hydroxy, C_{1-4} alkyloxy, nitro, amino, trifluoromethyl, hydroxy C_{1-4} alkyl, C_{1-4} alkyloxy C_{1-4} alkyl, amino C_{1-4} alkyl, mono- or di(C_{1-4} alkyl)amino C_{1-4} alkyl;

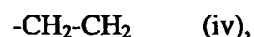
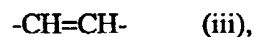
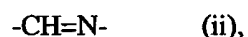
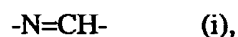
Het¹ represents a monocyclic or bicyclic heterocyclic radical; said monocyclic heterocyclic radical being selected from the group pyridinyl, piperidinyl, homopiperidinyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, triazolyl, pyranyl, tetrahydropyranyl, imidazolyl, imidazolyl, imidazolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, thiazolyl, thiazolidinyl, isothiazolyl, oxazolyl, oxazolidinyl, isoxazolyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, furanyl, tetrahydrofuran, thienyl, thiolanyl, dioxolanyl; said bicyclic heterocyclic radical being selected from the group quinolinyl, 1,2,3,4-tetrahydro-quinolinyl, isoquinolinyl, quinoxalinyl, quinazolinyl, phtalazinyl, cinnolinyl, chromanyl, thiochromanyl, 2H-chromenyl, 1,4-benzodioxanyl, indolyl, isoindolyl, indolinyl, indazolyl, purinyl, pyrrolopyridinyl, furanopyridinyl, thienopyridinyl, benzothiazolyl, benzoxazolyl, benzisothiazolyl, benzisoxazolyl, benzimidazolyl, benzofuranyl, benzothieryl; whereby each of said mono- or bicyclic heterocycle may optionally be substituted with one or where possible more substituents selected from halo, C_{1-4} alkyl, hydroxy, C_{1-4} alkyloxy, nitro, amino, trifluoromethyl, hydroxy- C_{1-4} alkyl, C_{1-4} alkyloxy- C_{1-4} alkyl, amino C_{1-4} alkyl, mono- or di(C_{1-4} alkyl)amino- C_{1-4} alkyl, aryl or aryl C_{1-4} alkyl;

Het² is the same as Het¹ and may also be a monocyclic heterocycle selected from piperazinyl, homopiperazinyl, 1,4-dioxanyl, morpholinyl, thiomorpholinyl; whereby each of said monocyclic heterocycle may optionally be substituted with one or where possible more substituents selected from halo, C_{1-4} alkyl, hydroxy, C_{1-4} alkyloxy, nitro, amino, trifluoromethyl, hydroxy C_{1-4} alkyl, C_{1-4} alkyloxy C_{1-4} alkyl, amino C_{1-4} alkyl, mono- or di-(C_{1-4} alkyl)amino C_{1-4} alkyl, aryl or aryl C_{1-4} alkyl;

R^6 represents hydrogen or C_{1-4} alkyl;

R^7 represents hydrogen or C_{1-4} alkyl; or

R^6 and R^7 taken together form a bivalent radical of formula $-R^6-R^7-$ wherein $-R^6-R^7-$ is :

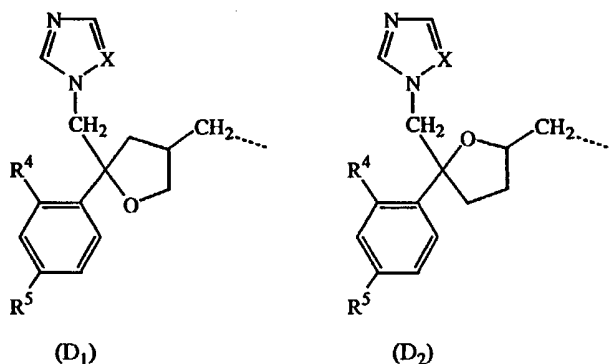


wherein one hydrogen atom in the radicals (i) and (ii) may be replaced with a

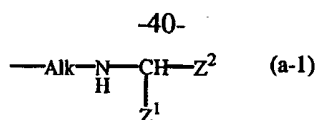
-39-

C₁₋₄alkyl radical and one or more hydrogen atoms in radicals (iii) and (iv) may be replaced by a C₁₋₄alkyl radical;

D represents a radical of formula



- 5 wherein X is N or CH;
 R⁴ is hydrogen or halo;
 R⁵ is halo.
2. A compound as claimed in claim 1 wherein D is a radical of formula D₁.
- 10 3. A compound as claimed in claim 1 or 2 wherein L is a radical of formula (a).
4. A compound as claimed in any one of claims 1 to 3 wherein Alk is 1,2-ethanediyl,
 1,2-propanediyl, 2,3-propanediyl, 1,2-butanediyl, 3,4-butanediyl, 2,3-butanediyl,
 2,3-pentanediyl or 3,4-pentanediyl.
- 15 5. A compound as claimed in any one of claims 1 to 4 wherein R¹ represents aryl, Het¹,
 or C₁₋₆alkyl optionally substituted with one, two or three substituents each
 independently selected from hydroxy, C₁₋₄alkyloxy, aryloxy, arylC₁₋₄alkyloxy, cyano,
 amino, mono- or di(C₁₋₄alkyl)amino, mono- or di(arylC₁₋₄alkyl)amino, C₁₋₄alkyloxy-
 carbonylamino, aminocarbonyl, aryl or Het²; R² represents hydrogen or C₁₋₆alkyl; or
 in case R¹ and R² are attached to the same nitrogen atom, they may also be taken
 together to form a heterocyclic radical selected from morpholinyl, pyrrolidinyl,
 piperidinyl or piperazinyl; said heterocyclic radical may optionally be substituted
 with C₁₋₄alkyl, aryl, arylC₁₋₄alkyl, hydroxyC₁₋₄alkyl, amino, mono- or di(C₁₋₄alkyl)-
 amino, mono- or di(C₁₋₄alkyl)aminoC₁₋₄alkyl or C₁₋₄alkyloxycarbonylamino; or R¹
 and R² may also be taken together to form an azido radical.
- 20 6. A compound as claimed in any one of claims 1 to 4 wherein L is a radical of formula



wherein Alk is 2,3-butanediyl, 2,3-pentanediyl or 3,4-pentanediyl;
 Z¹ is optionally substituted phenyl or optionally substituted phenylmethyl,
 isopropyl or *tert*-butyl;
 Z² is hydrogen, methyl or hydroxymethyl;

7. A compound as claimed in any one of claims 1 to 6 which is stereochemically pure.

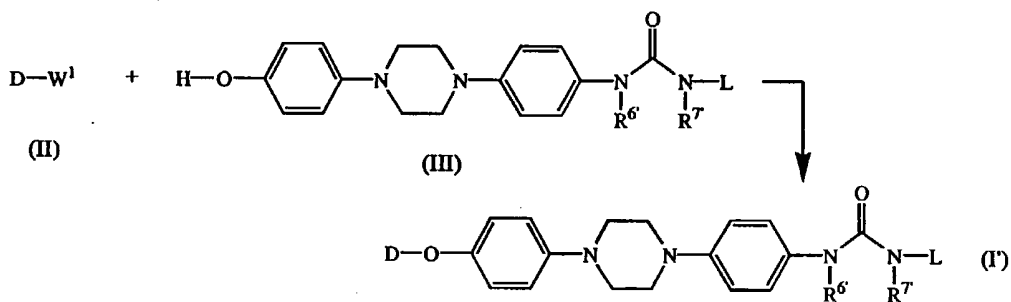
8. A compound as defined in any one of claims 1 to 7 for use as a medicine.

9. Use of a compound as defined in any one of claims 1 to 7 in the manufacture of a medicament for treating fungal infections.

10. A pharmaceutical composition comprising a pharmaceutically acceptable carrier, and as active ingredient a therapeutically effective amount of a compound as defined in any one of claims 1 to 7.

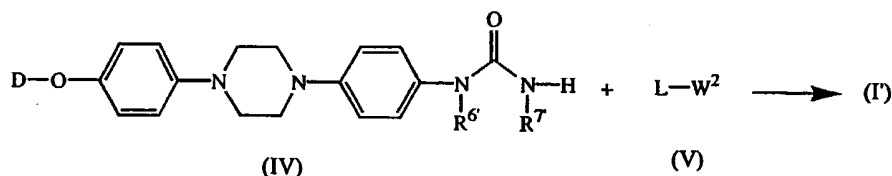
11. A process of preparing a compound of formula (I) wherein D and L are as defined in claim 1 and R⁶ and R⁷ are as defined as in claim 1 but other than hydrogen, said R⁶ and R⁷ being represented by R^{6'} and R^{7'} and said compound being represented by formula (I'), characterized by,

a) reacting an intermediate of formula (II) wherein W¹ is a suitable leaving group, with an intermediate of formula (III) in a reaction-inert solvent and in the presence of a suitable base;



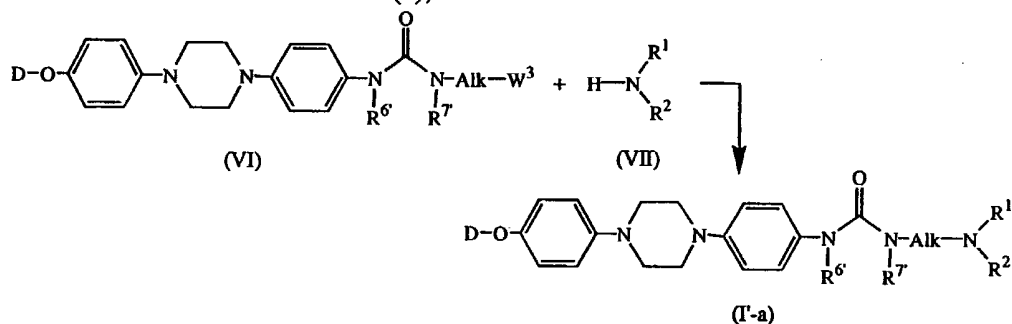
b) *N*-alkylating an intermediate of formula (IV) with an intermediate of formula (V) wherein W² is a suitable leaving group and wherein primary and secondary amines in L, in case they are present, are protected with a protective group P being a C₁₋₄alkyloxycarbonyl group, in a reaction-inert solvent and in the presence of a base; and in case L was protected, subsequently deprotecting L using art-known deprotection techniques;

-41-



c) reacting an intermediate of formula (VI) wherein W^3 is a suitable leaving group, with an intermediate of formula (VII) or NaN_3 optionally in the presence of a suitable base and optionally in a reaction-inert solvent; thus obtaining a compound of formula (I')

5 wherein L is a radical of formula (a);



and, if desired, converting compounds of formula (I') into each other following art-known transformations; and further, if desired, converting the compounds of formula (I'), into a therapeutically active non-toxic acid addition salt by treatment with an acid,
 10 or conversely, converting the acid addition salt form into the free base by treatment with alkali; and, if desired, preparing stereochemically isomeric forms or *N*-oxide forms thereof.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 99/03242

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D405/14 A61K31/495

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	A.K. SAKSENA ET AL.: "SCH 51048, a novel broad-spectrum orally active antifungal agent: synthesis and preliminary structure-activity profile" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 5, no. 2, 1995, pages 127-132, XP002082550 cited in the application *the whole document, especially page 128, formula 14*	1-11
A	WO 96 38443 A (SCHERING CORPORATION) 5 December 1996 (1996-12-05) cited in the application claims --- -/-	1-11

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

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"&" document member of the same patent family

Date of the actual completion of the international search

24 August 1999

Date of mailing of the international search report

02/09/1999

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 99/03242

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97 00255 A (SCHERING CORPORATION) 3 January 1997 (1997-01-03) cited in the application claims	1-11
A	WO 95 17407 A (SCHERING CORPORATION) 29 June 1995 (1995-06-29) cited in the application claims	1-11
A	WO 95 19983 A (JANSSEN PHARMACEUTICA N.V.) 27 July 1995 (1995-07-27) cited in the application claims	1-11

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 99/03242

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